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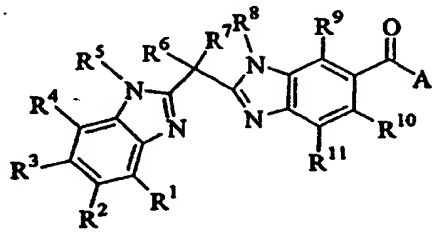

(I)

(57) Abstract

Bis–benzimidazole compounds of general formula (I) in which R^1, R^2, R^3 and R^4 are hydrogen, hydroxy or halogen, R^5 and R^8 are hydrogen, or (C_1–C_4)–alkyl,R^6 and R^7 are hydrogen, or (C_1–C_6)–alkyl, hydroxy, halogen, or (C_1–C_6)–alkoxy, R^9, R^{10} and R^{11} are hydrogen, halogen, nitro, cyano or trifluoromethyl, and A is a non–aromatic 5–7–membered N–heterocycle, etc, process for their preparation and their use for treating diseases associated with tryptase activity including allergic, inflammatory and related immunological diseases, in particular asthma, allergic rhinitis, allergic conjunctivitis and allergic dermatitis.

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DESCRIPTION

NEW BIS-BENZIMIDAZOLES

TECHNICAL FIELD

This invention relates to novel bis-benzimidazoles, processes for their preparation and their use for the prophylaxis and treatment of diseases associated with tryptase activity, in particular for the treatment of asthma and allergic rhinitis.

BACKGROUND ART

Human tryptase is a structurally unique and essentially mast cell specific trypsin like serine protease which has been suggested to play a central role in a number of mast cell mediated allergic and inflammatory diseases (Drugs of the Future 1996, 21, 811; Exp. Opin. Invest. Drugs 1997, 6, 811). The scope of this role is determined in part by the fact that mast cells are found widely distributed throughout the body as a heterogeneous and potentially site specific cell type (J. Leukoc. Biol. 1997, 61, 233-245; J. Exp. Toxic. Pathol. 1997, 49, 409-424). Elevated levels of tryptase have been detected in a number of diseases, including asthma, allergic conjunctivitis, allergic rhinitis, rheumatoid athritis, multiple sclerosis, and interstitial cystitis (Drugs of the Future 1996, 21, 811). Unlike other protease associated with mast cells, such as chymase, carboxypeptidase A, and cathepsin G, tryptase is present in virtually all mast cells including those in gut mucosa, alveolar interstitium, and dermis (Immunol. Res. 1989, 8, 130).

Tryptase is the major secretory proteinase in both the MC_{CT} and MC_T mast cell lines, which contain approximately 35pg and 11pg of the enzyme, respectively, per cell. This quantity of tryptase may represent up to 25% of the total protein content of the mast cell (J. Immunol. 1987, 138, 2611). Cloning and sequencing efforts have revealed that tryptase is comprised of a family of several highly conserved enzymes which share 90-98% sequence homology. The crystal structure of β-tryptase complexed with 4-amidinophenyl pyruvic acid has recently been reported (Nature 1998, 392, 306), which sheds significant light on the structure and unique biochemical properties of human tryptase. The active tetramer consists of a flat and nearly square assembly of monomers held together through hydrophobic surface contact interactions and heparin association. Each of the four monomer active sites faces the interior of an oval central cavity with the corresponding distances between adjacent active sites in the range of 20-

40 Å. The size of this central cavity and proximity of adjacent monomers limits accessibility of large protein substrates and inhibitors, making tryptase structurally well-suited for the task of selective neuropeptide and protein processing.

In broad terms, the scope of biochemical functions and the corresponding physiological consequences of tryptase proteolytic activity in vivo is defined by its substrate specificity, regulation, and by the complex distribution of mast cells throughout the body. The immediate consequence of mast cell stimulation and degranulation is the release of active β-tryptase along with other mediators, which then initiates the proteolytic cleavage of specific peptide and protein substrates. These substrates can by classified into three general types: neuropeptides, active daughter enzymes and zymogen proteins, and cell surface receptors, each of which may have complex biochemical and physiological significance.

The crystal structure of β-tryptase provides insight into the enzyme's unique substrate specificity and resistance to endogenous inhibitors. The central cavity of tryptase, which contains the active site domain, has limited accessibility due to the proximity and arrangement of adjacent monomers. This structural feature limits the substrate family to small, conformationally flexible peptides and to proteins which can project cleavable surface loops into the active site cavity and provides a rationale for the limited number of physiologically relevant tryptase substrates and inhibitors which have been identified.

The biological activities of tryptase in vitro can be divided into two main categories (Exp. Opin. Invest. Drugs 1997, 6, 811):

1. Cleavage of proteins/peptide substrates:

-Cleavage and inactivation of fibrinogen

-Degradation of vasoactive intestinal peptide (VIP), peptide histidine methionine (PHM), calcitonin gene-related peptide (CGRP) and kinetensin

-Activation of pro-urokinase, pro-MMP 3 (pro-matrix metalloprotease 3)

-Degradation of fibronectin

-Degradation of Type IV collagen

-Cleavage of 72 kDa gelatinase

-Generation of bradykinin from high and low molecular weight kininogen

-Activation of prekallikrein

2. Activation of cellular targets, cellular responses:

- Proliferation of fibroblasts, smooth muscle cells and epithelial cells
- Potentiation of histamine-induced bronchoconstruction
- Release of eosinophil cationic protein from eosinophils
- Histamine release from mast cells
- IL-8 production by epithelial cells
- Increased ICAM-1 expression on epithelial cells
- Signalling in human vascular endothelial cells via cleavage of PAR-2 (proteinase activated receptor)

Tryptase induced cytokine production or cellular degranulation by specific cell types. Tryptase stimulated interleukin-8 (IL-8) production by epithelial cells and stimulated histamine release from mast cells. Tryptase may also have direct effects on eosinophils, acting both as a chemoattractant and an inducer of the release of eosinophil cationic protein. These effects on mast cells and eosinophils may be particularly relevant in terms of the role of tryptase in asthma (Exp. Opin. Invest. Drugs 1997, 6, 811).

Researchers have also reported that tryptase effectively cleaves 72 kDa gelatinase, fibronectin and intact type IV collagen microfibrils (J. Cell. Biochem. 1992, 50, 337; Biochem. Biophys. Res. Commun. 1993, 191, 1230). The observed cleavage of gelatinase and fibronectin suggests that tryptase may function in the normal regulation of extracellular matrix turnover through a direct proteolytic mechanism. Such activity is important for tissue growth and remodeling, cell migration and wound healing and probably to tumor metastasis as well. Type IV collagen is proposed to link major elements of the extracellular matrix and is associated in particular with connective tissues. The degradation of type IV collagen may be of significance in certain pathological conditions involving the degradation and chronic inflammation of connective tissue and skin, such as arthritis, atopic dermatitis and psoriasis.

Another pathway by which tryptase may indirectly initiate extracellular matrix degradation is through the activation of matrix metalloproteinases (Exp. Opin. Invest. Drugs 1997, 6, 811). The cascade is likely initiated through the cleavage of prostromelysin or pro-matrix metalloproteinase 3 (proMMP-3) by tryptase. Once activated, MMP-3 can degrade proteoglycans, fibronectin and laminin as well as type IV and type IX collagen. Synovial procollagenase is activated by tryptase in vitro, and this activity is entirely dependent upon the enzymatic activation of MMP-3 (J. Clin. Invest. 1989, 84, 1657; J. Immunol. 1988, 140, 3936).

As a result, tryptase may function in a number of pathological conditions where MMP activity and cartilage degradation is involved, as well as at sites of collagen deposit in diseases such as arthritis, chronic peridontitis, rheumatiod synovium and sclerosis. More recent studies demonstrated a potential connection between tryptase activation of pro-matrix metalloproteinase-8 and bronchiectasis, a chronic lung disorder characterized by degradation of airway and lung tissue extracellular matrix (Eur. Respir. J. 1997, 10, 2788). In this study, a comparison of the bronchoalveolar lavage (BAL) fluid from subjects with bronchiectasis and healthy controls showed a strong correlation of tryptase activity with endogenous collagenase activation. These studies also demonstrated that the plasminogen activator-plasmin cascade, an alternative matrix degradation pathway, was down-regulated, supporting the importance of a tryptase-mediated MMP cascade in lung inflammatory disease.

Single-chain urinary type plasminogen activator (u-PA) is activated by tryptase and is also implicated in the degradation and remodeling of extracellular matrix including fibrinolysis, wound healing, and tumor metastasis (J. Biol. Chem.1994, 269, 9416-9419).

Tryptase has been shown to act as a mitogen for cultured human endothelial cells in vitro and may function in this context in the process of neovascularization (J. Allergy Clin. Immunol. 1998, 101, SllO). Thus, tryptase activity may be at the center of several physiological pathways that modulate cell growth and pathological conditions associated with hyperplasia.

The most direct evidence for the involvement of tryptase proteolytic activity in human asthma pathology has been obtained by Axys Pharmaceuticals Inc. using the tryptase inhibitor APC-366 in preclinical and clinical studies (Am. J. Respir. Crit. Care Med. 1995, 152, 2076; R&D Focus Drug News 18 May 1998). A recent phase IIa study was conducted with 16 mild asthmatics who were dosed with either placebo or a nebulized formulation of the tryptase inhibitor. During APC-366 dosing, subjects had a statistically significant improvement in overall mean area under the curve (AUC) for the late airway response of 33% ($p=0.012$) and a mean maximum fall in FEVl (forced expiratory volume in one second) of 21% ($p=0.007$) for LAR (late airway hyperresponsiveness), than compared to the results during placebo. Numerous reports of elevated mast cell tryptase levels in patients with seasonal allergic rhinitis and conjunctivitis and related allergic responses provide an compelling argument for the development of tryptase inhibitors for the treatment of allergic, inflammatory and related immunological diseases (Brit. J. Anaesthesia 1998, 80, 26; Clin. Exp. Allergy 1998, 28, 83; Allergy 1997, 1102, 52; Clin. Exp. Allergy 1998, 28, 220; Ophthalmology 1997, 104, 849-853).

A number of further diseases or conditions are thought to be mediated by tryptase

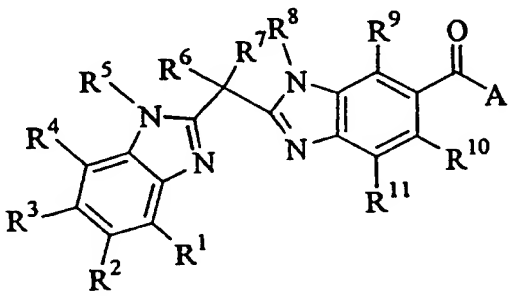
activity. These include: metastasis of tumor cells (Drugs of the Future 1996, 21, 811), anaphylaxis, mastocytosis, scleroderma, skin diseases such as urticaria, atopic dermatitis, bullous pemphigoid, psoriasis (Exp. Opin. Invest. Drugs 1997, 6, 811), pulmonary fibrosis, interstitial pneumonia, nephritis, hepatic fibrosis, hepatitis, hepatic cirrhosis, Crohn's disease, ulcerative colitis, nasal allergy, peptic ulcers, gastric disease induced by non-steroidal inflammatory agents, cardiac infarction, disseminated intravascular coagulation, pancreatitis, multi organ failure (WO 9737969), interstitial lung diseases, gingivitis, peridontitis, virus infections (e.g. influenza virus, Sendai virus, human immunodeficiency virus), breast cancer (Structure 1997, 5, 1465), ocular allergy (including atopic, vernal and giant papillary keratoconjunctivitis, contact blepharoconjunctivitis, Exp. Opin. Invest. Drugs 1998, 7, 27), bladder cancer (Histochemical J. 1997, 29, 759), fibrotic diseases such as fibrotic lung disease, artherosclerosis, and cardiomyopathic disorders (J. Immunol. 1997, 158, 2310; FASEB J. 1998, 12, A434), syncytial virus infections (J. Med. Chem. 26, 294 (1983)) and diseases in which matrix metalloproteases are activated (Current Pharm. Design, 1997, 3, 45; Current Pharm. Design 1996, 2, 624; Exp. Opin. Ther. Patents 1995, 5, 1087).

Tryptase inhibitors have been described in WO 9737969, WO 9609297 and WO 9420527. The new bis-benzimidazoles are tryptase inhibitors which interact with the catalytic Ser and His residues through the intermediacy of divalent zinc as described by Katz et al. (Nature 1998, 391, 608). Even low concentrations of ambient zinc will enhance the potency of these inhibitors substantially in vitro (Angew. Chem. 1998, 110, 1939).

DISCLOSURE OF INVENTION

The invention relates to novel bis-benzimidazoles, processes for their preparation and their use for the prophylaxis and treatment of diseases associated with tryptase activity, including allergic, inflammatory and related immunological diseases, in particular for the treatment of asthma, allergic rhinitis, allergic conjunctivitis and allergic dermatitis.

The invention relates to compounds of the general formula (I) and their tautomeric and stereoisomeric forms



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or halogen,

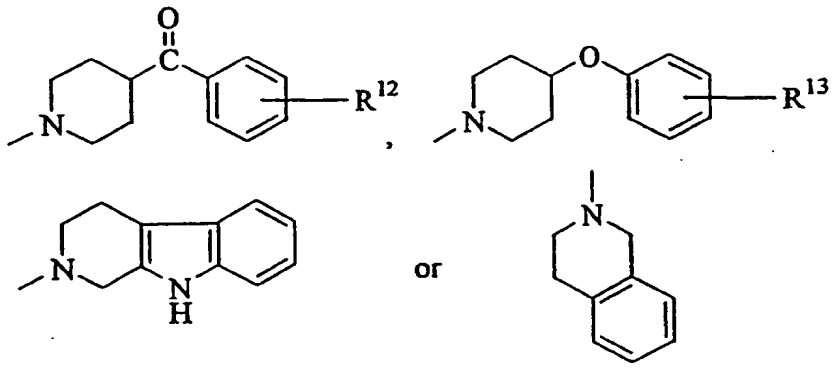
R^5 and R^8 are identical or different and represent hydrogen, or straight-chain or branched (C_1-C_4)-alkyl,

R^6 and R^7 are identical or different and represent hydrogen, straight-chain or branched (C_1-C_6)-alkyl, hydroxy, halogen, or straight-chain or branched (C_1-C_6)-alkoxy,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen, halogen, nitro, cyano or trifluoromethyl,

and

A represents a residue of a formula



wherein

R^{12} and R^{13} are identical or different and denote hydrogen, halogen, nitro, cyano, straight-chain or branched (C_1 - C_6)-alkyl or (C_1 - C_6)-alkoxy, or hydroxy,

or

A represents a non-aromatic 5- to 7-membered N-heterocycle which is bound over the nitrogen atom and which optionally contains an oxygen atom or a residue -NR^{14} or -CH-R^{15},

wherein R^{14} and R^{15} are identical or different and denote hydrogen, (C_3 - C_8)-cycloalkyl, or denotes straight-chain or branched (C_1 - C_4)-alkyl, which is optionally substituted by (C_6 - C_{10})-aryl,

or denote (C_6 - C_{10})-aryl or a 5- or 6-membered aromatic or non-aromatic heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O, and which, in the case of the non-aromatic heterocycle, is optionally bound over a nitrogen atom and wherein the aryl and the heterocycle are optionally mono- to tri-substituted by

identical or different substitutents from the series comprising halogen, nitro, cyano, hydroxy, trifluormethyl or a residue of the formula $-NR^{16}R^{17}$,

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched (C_1- C_4)-alkyl or (C_1 - C_4)-acyl, or a residue $-SO_2-CF_3$, or R^{16} and R^{17} form together with the nitrogen atom a non-aromatic 5- to 7-membered heterocycle, optionally having a further oxygen atom or a residue -NH,

or

R^{14} denotes a residue of the formula $-SO_2-R^{18}$,

in which

R^{18} denotes (C_6 - C_{10})-aryl, or straight-chain or branched (C_1 - C_4)-alkyl,

or

A represents a residue of the formula $-NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen, straight-chain or branched (C_1 - C_4)-alkyl,

R^{20} denotes a residue of a formula -D-E-R^{21},

in which

D denotes a straight-chain or branched (C_1 - C_6)-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes (C_6 - C_{10})-aryl or a 5- or 6-membered aromatic heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O,

which are optionally mono- to tri-substituted by nitro, cyano, halogen, tetrazolyl or by a residue of the formula $-NR^{22}R^{23}$,

in which

R^{22} and R^{23} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_6)-acyl or (C_1 - C_6)-alkyl, or R^{22} denotes hydrogen and R^{23} denotes a residue $-SO_2-CF_3$.

The new bis-benzimidazoles according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here. Physiologically acceptable salts are preferred in the context of the present invention.

Physiologically acceptable salts can also be salts of the compounds according to the

invention with inorganic or organic acids. Preferred salts here are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, ethanesulphonic acid, berzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemate forms, as well as the diastereomer mixtures. The racemate forms, like the diastereomers, can be separated into the stereoisomerically uniform constitutents in a known manner.

A non-aromatic 5- to 7-membered heterocycle in general represents morpholinyl, piperidinyl, piperazinyl or 1,4-diazacycloheptyl.

The following are mentioned as preferred: piperidinyl, piperazinyl or 1,4-diazacycloheptyl.

Heterocycle in general represents a 5- to 7-membered aromatic or non-aromatic, preferably 5- to 6- membered, saturated or unsaturated ring which can contain up to 3 oxygen, sulphur and/or nitrogen atoms as heteroatoms.

The following are mentioned as preferred: thienyl, furyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazolyl, dihydrothiazolyl, isothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, oxazolinyl or triazolyl.

Preferred compounds of the general formula (I) are those,

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or fluorine,

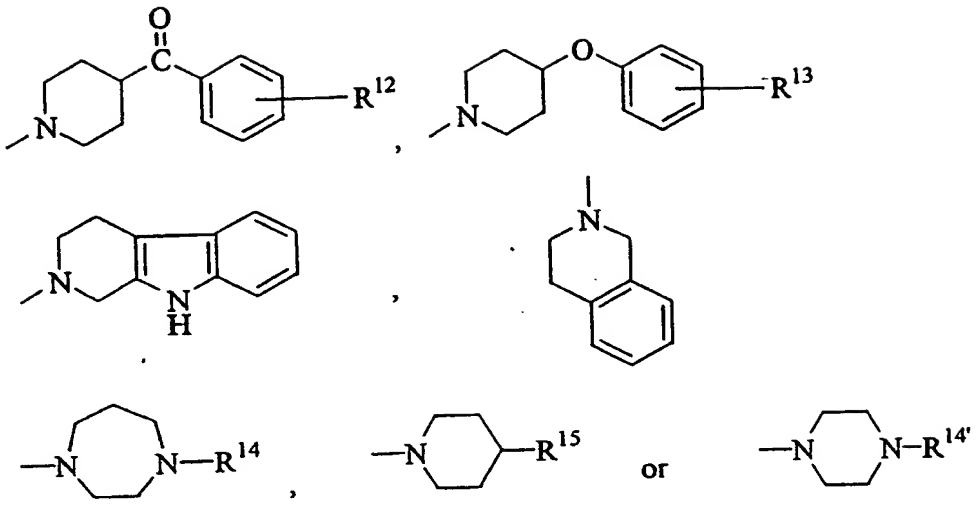
wherein at least one of the above mentioned substituents R^1, R^2, R^3 or R^4 is different from hydrogen,

R^5 and R^8 are identical or different and represent hydrogen, methyl, ethyl or isopropyl,

R^6 and R^7 are identical or different and represent hydrogen, straight-chain or branched (C_1-C_4)-alkyl, hydroxy, or fluorine,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen, fluorine, chlorine or cyano, and

A represents a residue of the formula



wherein

R^{12} and R^{13} are identical or different and denote hydrogen, fluorine, chlorine or cyano,

R^{14}, $R^{14'}$ and R^{15} are identical or different and denote hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or denote straight-chain or branched $(C_1 - C_3)$-alkyl, which is optionally substituted by phenyl,

or denote phenyl, pyrimidyl, pyridyl or piperidinyl which are optionally substituted by fluorine, chlorine, nitro, cyano or a residue of the formula $-NR^{16}R^{17}$,

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched $(C_1 - C_3)$-alkyl or $(C_1 - C_3)$ acyl, or a residue $-SO_2-CF_3$.

or

$R^{14'}$ denotes a residue of the formula $-SO_2-R^{18}$,

in which

R^{18} denotes phenyl, or straight-chain or branched $(C_1 - C_3)$-alkyl,

or

A represents a residue of the formula $-NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen, or straight-chain or branched $(C_1 - C_3)$-alkyl

and

R^{20} denotes a residue of the formula D-E-R^{21},

in which

D denotes a straight-chain or branched (C_1 - C_5)-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes phenyl or pyridyl, which are optionally monosubstituted or disubstituted by nitro, cyano, fluorine, chlorine, tetrazolyl or by a residue of the formula $-NR^{22}R^{23}$, in which

R^{22} and R^{23} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_3)-acyl, or R^{22} denotes hydrogen and R^{23} denotes a residue $-SO_2-CF_3$.

Particularly preferred compounds of the general formula (I) are those,

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or fluorine,

wherein two or three of the above mentioned substituents R^1, R^2, R^3 or R^4 are different from hydrogen,

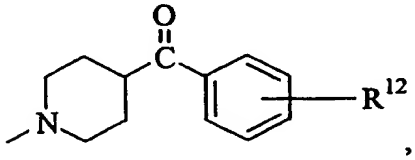
R^5 and R^8 are identical or different and represent hydrogen, methyl or isopropyl,

R^6 and R^7 are identical or different and represent hydrogen, straight-chain or branched (C_1 - C_3)-alkyl, hydroxy, or fluorine,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen or fluorine,

and

A represents a residue of the formula



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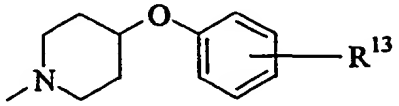

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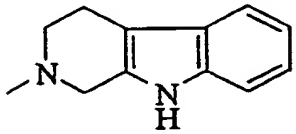

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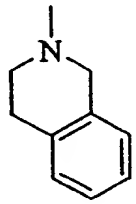

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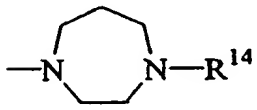

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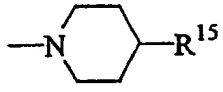

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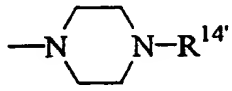


wherein

R^{12} and R^{13} are identical or different and denote hydrogen or fluorine

and

R^{14}, $R^{14'}$ and R^{15} are identical or different and denote hydrogen, cyclopentyl, cyclohexyl, cycloheptyl, or denote straight-chain or branched (C_1 - C_3)-alkyl, which is optionally substituted by phenyl, or denote phenyl, pyrimidyl, pyridyl or piperidinyl, which are optionally substituted by fluorine, nitro, cyano or a residue of the formula -$NR^{16}R^{17}$,

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_3)-alkyl, or a residue -SO_2-CF_3.

or

$R^{14'}$ denotes a residue of the formula -SO_2-R^{18},

in which

R^{18} denotes phenyl or methyl,

or

A represents a residue of the formula -$NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen or methyl

and

R^{20} denotes a residue of the formula -D-E-R^{21},

in which

D denotes a straight-chain or branched (C_1 - C_4)-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes phenyl or pyridyl, which are optionally monosubstituted or disubstituted by nitro, cyano, fluorine, tetrazolyl or by a residue of the formula -$NR^{22}R^{23}$,

in which

R^{22} and R^{23} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_3)-acyl, or R^{22} denotes hydrogen and R^{23} denotes a residue -SO_2-CF_3.

Very particularly preferred compounds of the general formula (I) are those,

in which R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen or fluorine,

wherein two or three of the above mentioned substitutents R^1, R^2, R^3 or R^4 are different from hydrogen,

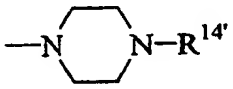
R^5 denotes hydrogen and R^8 denotes methyl,

R^6 and R^7 are identical or different and represent hydrogen, methyl or fluorine,

R^9, R^{10} and R^{11} are hydrogen,

and

A represents a residue of the formula



wherein

$R^{14'}$ denotes phenyl, which is optionally substituted by fluorine, cyano or a residue $-NHSO_2CF_3$.

or

A represents a residue of the formula $-NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen,

R^{20} denotes a residue of the formula -D-E-R^{21},

in which

D denotes $(CH_2)_2$-group,

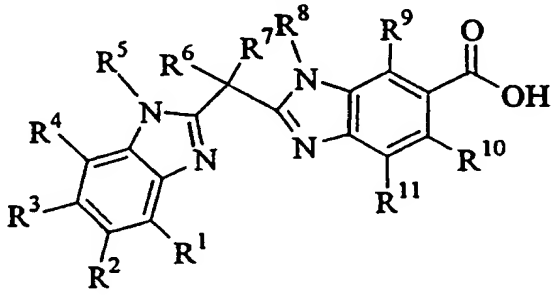
E denotes an oxygen atom

and

R^{21} denotes phenyl, which is optionally monosubstituted or disubstituted by fluorine or cyano.

Processes for the preparation of compounds of the general formula (I) have additionally been found characterized in that

[A] compounds of the general formula (II)



(II)

in which

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} have the above mentioned meaning,

or their reactive derivatives on the carboxyl radical

are reacted with compounds of the general formula (III)

$$A-H \qquad (III)$$

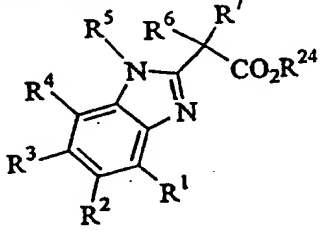
in which

A has the above mentioned meaning,

in inert solvents, if appropriate in the presence of a base and/or in the presence of auxiliary reagents,

or

[B] compounds of the general formula (IV)

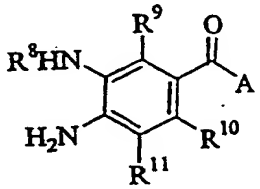


(IV)

in which

R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the above mentioned meaning, and R^{24} denotes straight-chain or branched (C_1 - C_6)-alkyl,

are reacted with compounds of the general formula (V)



(V)

in which

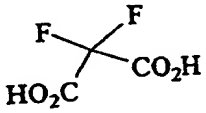
R^8, R^9, R^{10}, R^{11} and A have the above mentioned meaning,

in inert solvents, if appropriate in the presence of a base and/or in the presence of auxiliary reagents,

or

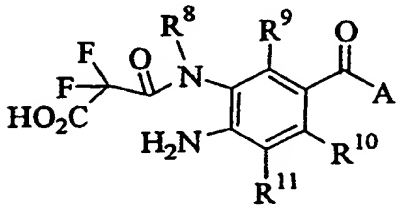
[C] in the case of R^6/R^7 = F,

first compounds of the general formula (V) are reacted with a compound of the formula (VI)

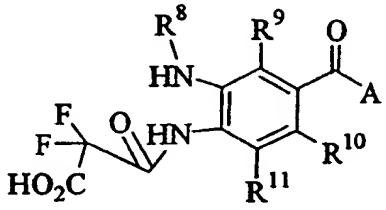


(VI)

together with the system consisting of reagents which can facilitate this reaction in inert solvents, preferably with the system PyBroP, HOBt and NMM and in dimethylformamide to prepare compounds of the general formulae (VIIa and/or VIIb)



(VIIa)

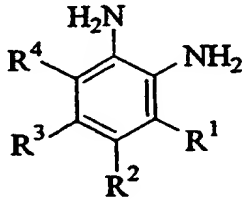


(VIIb)

in which

R^8, R^9, R^{10}, R^{11} and A have the above mentioned meaning,

and in the second step are reacted with compounds of the general formula (VIII)



(VIII)

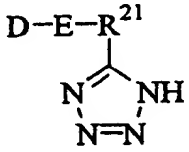
in which

R^1, R^2, R^3 and R^4 have the above mentioned meaning,

with the above mentioned system and finally with acetic acid,

or

[D] in the case where A in the general formula (I) is a residue of the formula $-NR^{19}R^{20}$ in which R^{19} is hydrogen and R^{20} is a residue of the following formula

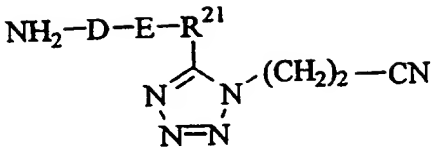


in which

D, E and R^{21} have the above mentioned meaning,

the compounds of the general formula (II) mentioned above or their reactive derivatives on the carboxyl radical

are reacted in inert solvents with compounds of the general formula (IX)

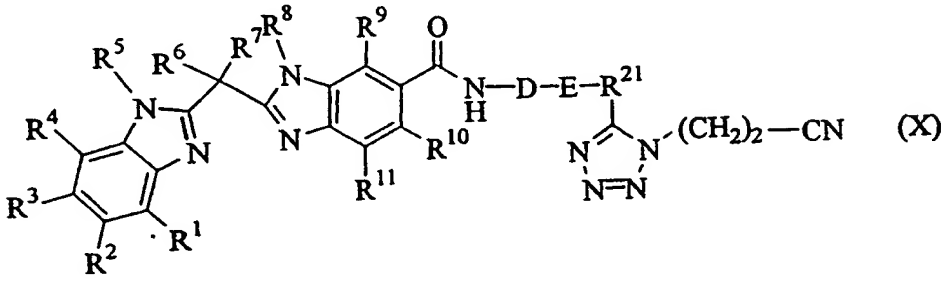


(IX)

in which

D, E and R^{21} have the above mentioned meaning,

together with appropriate reagents for amidation, preferably with the system WSCI HCI, HOBt and NMM to prepare compounds of the general formula (X)



(X)

in which R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{21}, D and E have the above mentioned meaning,

and in the last step the residue $-(CH_2)_2-CN$ is eliminated in the presence of a base, preferably DBU (1,8-diazabicyclo[5.4.0]undec-7-ene),

or

[E] in the case of R^6 = F or OH and R^7 = alkyl, compounds of the general formula (I) in which R^6 = H and R^7 = alkyl are reacted first in the system $NaIO_4$ /$RuCl_3$ in inert solvents such as water and tetrahydrofuran to prepare compounds of the general formula (I), in which R^6 = OH, and in the second step are reacted with Et_3NSF_3 in inert solvents such as CH_2Cl_2 to prepare the fluorine substituted derivatives,

and in the case of R^5 and/or R8 ≠ hydrogen an alkylation takes place optionally.

Processes according to the invention can be illustrated by way of example by the following equations:

EDC or WSCI HCI: N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

NMM: N-methylmorpholine

HOBt: 1-hydroxy-benzotriazole

DMPU: 1,3-dimethyltetrahydro-2(1H)-pyrimidone

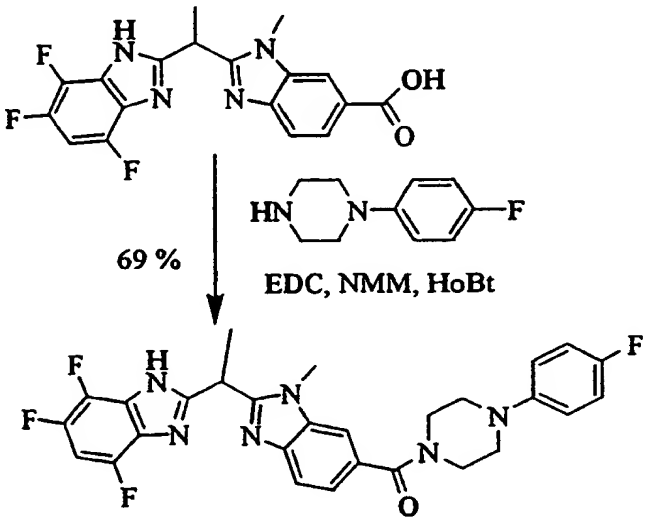
PyBOP: benztriazol-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate

PyBroP: bromo-tris-pyrrolidinophosphonium hexafluorophoshate

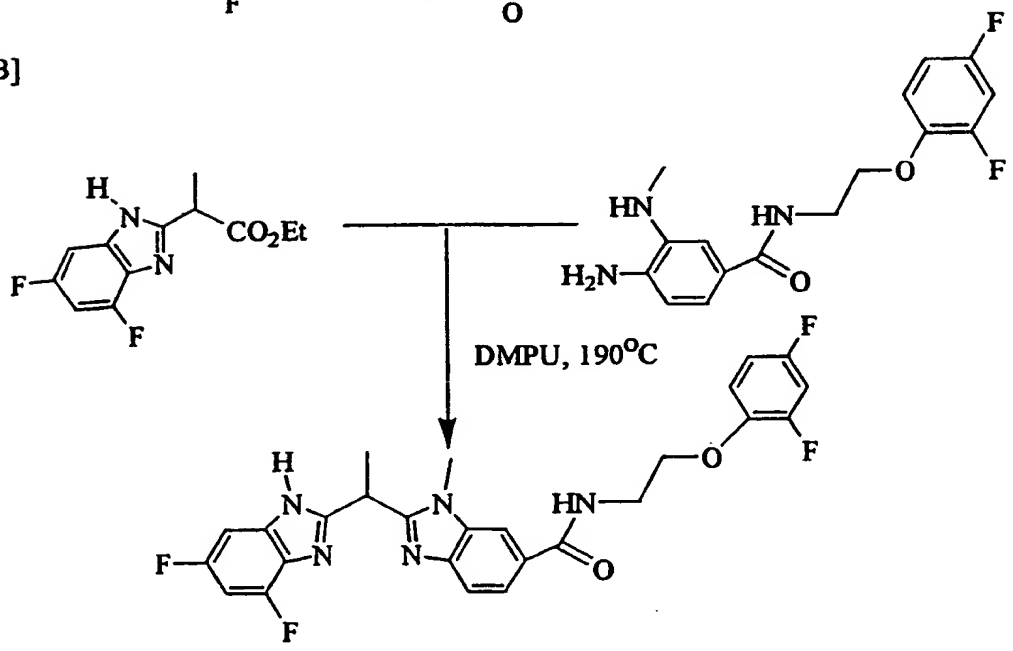
TBTU: O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate

DEAD: diethyl azodicarboxylate

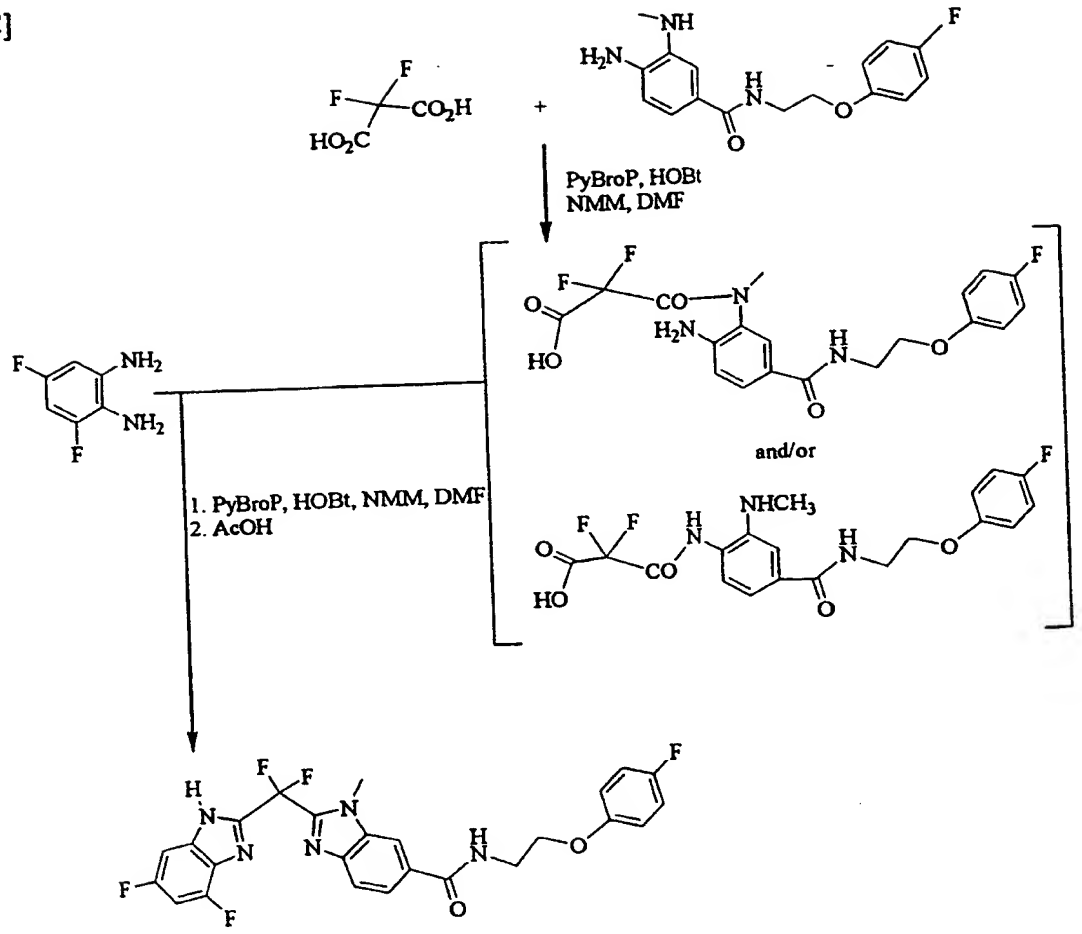
[A]



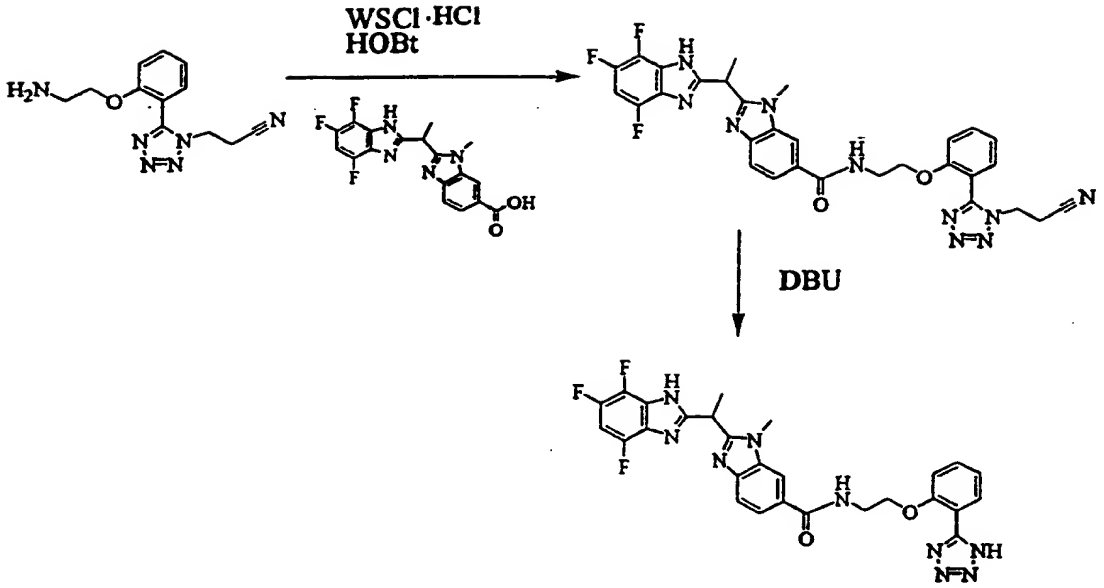
[B]



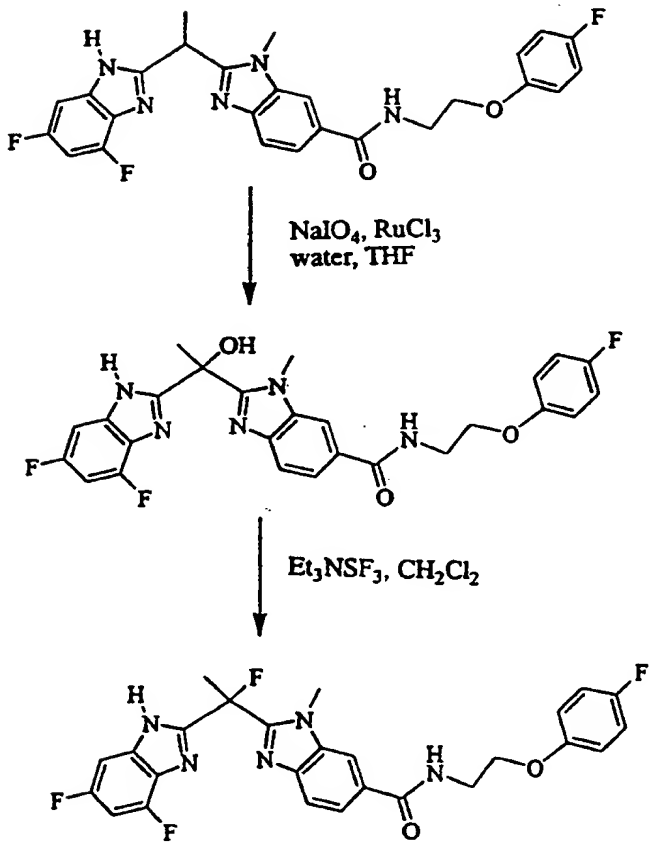
[C]



[D]



[E]



Process [A]

Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofuran, acetone, dimethyl sulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Dichloromethane and dimethylformamide are preferred.

Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogencarbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (trialkyl (C_1-C_6)amines) such as triethylamine, or N-methyl- or ethylmorpholine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or amides such as sodium amides, lithium butyl amide or butyllithium, pyridine or methylpiperidine. Triethylamine, N-methylmorpholine or N-ethylmorpholine are preferred.

The process is in general carried out in a temperature range from -30 °C to +100 °C, preferably from -10 °C to +50 °C.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formula (II) or (III).

Process [B]

Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such di-n-butyl ether, dimethyl sulfoxide, dimethylformamide or DMPU or DMEU (N, N-dimethylethyleneurea) or high-boiling aromatic carbocyclic or heterocyclic compounds such as mesitylene. Preferred are DMPU and dimethylformamide.

The process is in general carried out in a temperature range from 30 °C to 300 °C, preferably from 100 °C to 250 °C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5

bar).

Process [C]

Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofuran, acetone, dimethyl sulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Dichloromethane is preferred.

Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogencarbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (trialkyl (C_1-C_6) amines) such as triethylamine, or N-methyl- or N-ethylmorpholine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or amides such as sodium amides, lithium butyl amide or butyllithium, pyridine or methylpiperidine. Triethylamine, N-methylmorpholine or N-ethylmorpholine are preferred.

The process is in general carried out in a temperature range from -30°C to +100°C, preferably from -10 °C to +50 °C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The base is employed in an amount from 1 mol to 10 mol, preferably from 1 mol to 4 mol, relative to 1 mol of the compounds of the general formula (VIIa) or (VIIb).

Process [D]

Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofuran acetone, dimethyl sulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Dichloromethane is preferred.

Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogen carbonate or

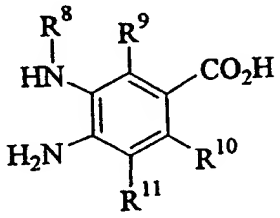
potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (trialkyl (C_1-C_6) amines) such as triethylamine, or N-methyl- or N-ethylmorpholine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or amides such as sodium amides, lithium butyl amide or butyllithium, pyridine or methylpiperidine. Triethylamine, N-methylmorpholine or N-ethylmorpholine are preferred.

The process is in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formula (II) or (1X).

Compounds of the general formula (II) are new and can be prepared by reaction of compounds of the general formula (IV) with compounds of the general formula (XI)



(XI)

in which

R^8, R^9, R^{10}, and R^{11} have the above mentioned meaning,

in presence of one of the above mentioned solvents, preferably dimethylformamide and DMPU at 190°C.

Compounds of the general formula (XI) are known (CAS No. 66630-74-8) or can be also prepared by reduction of nitro substituted compounds in the system H_2/Pd/C in methanol.

Compounds of the general formula (III) are known or can be prepared like described above.

Compounds of the general formula (VIII) are known (J. Fluorine Chem. 18, 1981, 507, J. Med. Chem. 1555, 38, 4906).

Compound of the formula (IV) is known (J. Fluorine Chem. 49, 1990, 275).

Compounds of the general formula (V) are kn wn or new and can be prepared by

reaction of compounds of the general formula (XII)

$$H_2N\text{-}D\text{-}E\text{-}R^{21} \qquad (XII)$$

in which

D, E and R^{21} have the above mentioned meaning,

with compounds of the general formula (XI) in the system PyBOP, HOBt, NMM and DMF.

The process is in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

The process is generally carried out at normal pressure. However, it is also possible to carry it out at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

Compounds of the general formula (XII) are generally known or can be prepared by common methods.

Compounds of the general formula (IX) are new and can be prepared by reaction of compounds of the general formula (XIII)

$$t\text{-}BuO\text{-}CO\text{-}NH\text{-}D\text{-}E\text{-}R^{21}\text{-}COOH \qquad (XIII)$$

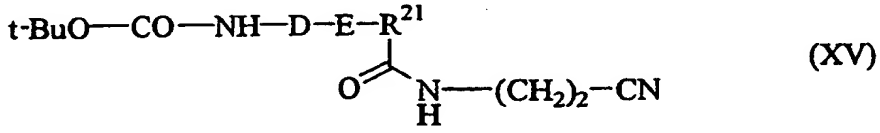
in which

D, E and R^{21} have the above mentioned meaning,

with a compound of the formula (XIV)

$$NH_2\text{-}(CH_2)_2\text{-}CN \qquad (XIV)$$

in the system TBTU in the presence of triethylamine to prepare compounds of the general formula (XV)

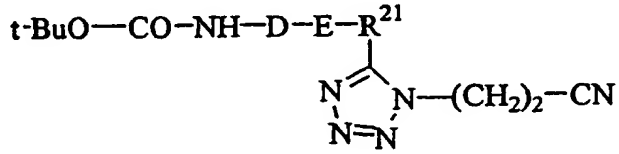


(XV)

in which

D, E and R^{21} have the above mentioned meaning,

and in the second step with Ph_3P/DEAD and $TMSN_3$ to prepare compounds of the general formula (XVI)



(XVI)

in which

D, E and R^{21} have the above mentioned meaning,
and in the last step by eliminating the tert-butyloxycarbonyl group with HCl/1,4-Dioxane.

Compounds of the general formula (XIII) are known or can prepared as described in Z. Naturforsch. B, 45, 1990, 817.

Compounds of the general formula (X) are new and can be prepared as described above.

Biological Protocols

The efficacy of the compounds of the present invention for the treatment of the vast majority of immunomediated inflammatory disorders can be evaluated by either in vitro or in vivo procedures. Thus, the anti-inflammatory efficacy of the compounds of the present invention can be demonstrated by assays well known in the art, for example, the Reversed Passive Arthus Reaction (RPAR)-PAW technique (see, e.g., Gangly et al. (1992) U.S. Patent No. 5,126,352).

Assays for determining the therapeutic value of compounds in the treatment of various skin conditions, such as hyperproliferative skin disease, are well known in the art, for example, the Arachidonic Acid Mouse Ear Test (ld.). The compounds of the present invention can be evaluated for their antiulcer activity according to the procedures described in Chiu et al. (1984) Archives Internationales de Pharmacodynamie et de Therapie 270: 128-140. The efficacy of the compounds of the present invention in blocking cell fusion caused by a syncytial virus infection can be evaluated by the methods generally set forth in Tidwell, et al., J. Med. Chem. 26.. 294-298 (1983).

Inhibitory activities of the compounds of the invention against human tryptase may be determined as described below.

In vitro Tryptase Inhibition Assay

The inhibitory activity against human tryptase was determined according to WO 9822619.

The following protocol represents an assay for determination of inhibition in the presence of 150 μM zinc chloride:
Tryptase solution (60 g/mL) was prepared by dissolving tryptase purified from human lung or

skin tissue preparations or human mast cell line (HMC-1) or obtained from commercial sources, e.g., ICN Biomeidals, Irvine, California, Athens Research & Technology, Athens, Georgia, etc., in a solvent mixture comprising: 10 mM 2-N-morpholinoethane sulfonic acid, 2 mM $CaCl_2$, 20% glycerol and 50 g/mL heparin. Substrate solution containing 2 mM synthetic tripeptide (tosyl-Gly-Pro-Lys-p-nitroanilide) was obtained from Sigma. Test Compound solutions were prepared by diluting a stock solution (1 mg of test Compound in 200 μL of dimethyl sulfoxide (DMSO) by ten-fold into assay buffer (comprising: Tris-HCI (pH 8.2), 50 mM; NaCl, 100 mM; 0.05% polyoxyethylenesorbitan monolaurate (Tween-20: trade name); and zinc chloride, 150 μM) and then making seven additional three-fold dilutions into 10% DMSO in assay buffer.

Aliquots (50 μL) from each of the eight dilutions of test compound solution were added to separate wells in a 96-well U-bottom microtiter plate. Typtase solution (25 μL) was added to each well and the solutions were mixed for 1 hour at room temperature. Substrate solution (25 μL) was added to initiate the enzymatic reaction and the microtiter plates were immediately transferred to a UVMAX Kinetic Microplate Reader (Molecular Devices). The hydrolysis of the chromogenic substrate was followed spectrophotometrically at 405 nanometers for five minutes. Initial velocity measurements were calculated from the progress curves by kinetic analysis program (BatchKi; Petr Kuzmic, University of Wisconsin, Madison, WI). Apparent inhibition constants (Ki') were calculated from the enzyme progress curves using standard mathematical models.

Proceeding as described in this application or by methods known to those of ordinary skill the following compounds of the invention were tested for tryptase inhibitory activity and the following Ki' values were obtained:

Example No.	Ki' (nM)
4	16.9
5	65.3
6	3.0
9	11.1
11	4.7
13	4.4
17	14.0
18	6.1
21	7.5
22	5.3
24	9.0
33	7.7
40	42
47	13
52	9.0
60	4.6

The assay protocol for determination of inhibition in the absence of zinc is conducted under essentially equivalent assay conditions that described above, with the exception that the assay medium does not contain zinc chloride and is modified to l mM EDTA. Following these assay conditions none of the compounds of the invention showed inhibitory activity with Ki' values lower than 10 μM.

Proceeding as in the above assay the compounds of the invention were also tested for their inhibitory activity toward plasmin, trypsin and thrombin in the presence of 150 μM zinc chloride. Following these assay conditions the compounds of the invention showed inhibitory activities, which were at least 10^2, typically 10^3 to 10^5 times greater than the inhibitory activity toward tryptase.

Primate Acute Asthma Model

An primate acute asthma model was employed for the in vivo evaluation of the compounds of the invention as antiasthmatics.

Introduction

One aspect of the model is that following an inhaled antigen challenge (Ascaris suum extract), there is an acute bronchoconstriction which peaks after 2-3 minutes and generally resolves within 60 minutes. 24 Hours later the primate airways have become hyperresponsive. This is measured by assessing the responsiveness of the lungs to an inhaled methacholine challenge. Furthermore, a bronchoalveolar lavage carried out at this time will show evidence of a large cellular influx, the predominant cell being the eosinophil.

The treatments (vehicle or drug treatments) are administered prior to the antigen challenge, the route of administration and dosing regime will vary according to the type of compound being studied. Potential therapeutic compounds can be tested in this model to see whether they can prevent or reduce the increase in lung resistance, airway hyperresponsiveness and inflammatory cell influx into the airways.

Method

Animals: Male cynomolgus monkeys (Macaca fascicularis) were used in the development of this model. The animals were maintained at constant temperature and humidity, with a twelve hour light cycle. They were fed twice daily, except on an experimental day when food was withheld the night before the procedure. Water was available ad lib at all times.

Experimental Procedure: On each experimental day animals were anaesthetised with a ketamine/xylazine mixture (70:12 mg kg^{-1} @ 0.1 ml kg^{-1}) while still in their cage. When unconscious they were brought into the primate laboratory where they were placed in a supine position on a heated water blanket on a trolley. Ophthalmic ointment was wiped onto each eye, and 0.2 ml lidocaine (2%), sprayed onto the larynx and over the back of the throat. The jaws were held apart by a jaw spreader and a cuffed 5.0 gauge endotracheal tube (with the end liberally smeared with xylocaine gel, 2%) was inserted with the aid of laryngoscope. The animal was then placed into a specially designed restraint chair such that the animal was in a slightly reclined but upright sitting position, secured only by a collar at the neck. A water heated blanket surrounded the animal.

The endotracheal tube was connected to a Harvard Ventilator adjusted to deliver 30-35 breaths per minute. Airflow was measured by a Fleisch pneumotachograph and thoracic pressure was measured by a validyne pressure transducer (as the difference between the pressure at the distal end of the tube and room pressure).

The pneumotachograph and validyne were connected to a pre-amplifier and then into an MI^2 respiratory analyzer. Using the primary signals of flow and pressure the analyzer computed airway resistance and compliance (as well as a number of other respiratory parameters). An initial measurement of 5-6 minutes was carried out to ensure the signals were steady and that the values for resistance and compliance were within recognized limits.

Ascaris challenge: Following this an inhalation challenge with Ascaris suum was carried out. The aerosol was delivered with a pressure driven Rainbow drop nebuliser (puritan-Bennett) connected to a Bird mark 7A respirator, set to deliver 15 breaths per minute. 30 Breaths of antigen were administered after which the acute bronchoconstriction was monitored for 15 min. The normal dose of antigen nebulised was a solution containing 1000 µg/ml of ascaris extract. However this dose of antigen could be titrated such that the increase in resistance should be in the range of 100-200% above baseline. If the bronchoconstriction is much higher then the inflammation induced may be too great to treat.

After the challenge had been finished the animal was weaned off the ventilator, and when he could breath for himself was released from the restraint chair and laid supine on the trolley. When the normal reflexes (eye blink, swallow) had returned, along with muscle tone in the limbs the animal was returned to its cage.

Bronchoalveolar lavage: A bronchoalveolar lavage was carried out both before the antigen challenge (giving a baseline reading) and again following the methacholine dose response curve 24 hours later. The distal end of a paediatric fibreoptic bronchoscope was liberally coated with xylocaine gel, and inserted down the endotracheal tube. The bronchoscope was guided past the carina into one side of the lung and onward into the distal lung until the tip of the bronchoscope was wedged in the bronchoalveolar region. Then 15 ml of normal saline at room temperature was instilled slowly down one channel of the bronchoscope followed by 2 - 3 ml of air to ensure complete emptying of the bronchoscope channel. The fluid was then slowly aspirated back into the syringe using gentle pressure and gentle movement of the tip of the bronchoscope. Typically, recovery volumes were greater than 60% of the instilled volume. The recovered volume was measured and put into a 15 ml falcon tube and stored on ice for subsequent treatment. The lavage fluid was centrifuged at 1100 rpm for 10 min at 4°C. The supernatant was pipetted off and frozen at -20°C for later analysis. The cell pellet was resuspended in Hanks Balanced Salt Solution (HBSS; calcium and magnesium-free) and

aliquots were used for total cell counts (Coulter counter) and cell differential counts (Cytospin preparations).

Methacholine Challenge: Methacholine dose response curves were carried out to assess the airway hyperresponsiveness. In the acute model, the hyperresponsiveness was assessed at +24 hour and compared to the responsiveness 7 days before treatment. An aerosol of phosphate buffered saline (PBS) was delivered using a nebuliser as above. The aerosol was administered for 15 breaths and then lung resistance was monitored for ten minutes. Methacholine (0.1 $mg.ml^{-1}$, 15 breaths) was administered followed by another ten minutes monitoring. Successive doses of methacholine were administered with the dose increasing by a half-log at each step until either the lung resistance had doubled or the maximum dose of methacholine (100 $mg.ml^{-1}$) had been administered. The baseline (zero%) resistance was taken as the resistance achieved following the PBS administration. The increase in lung resistance (%) and the methacholine doses were entered into a spreadsheet and the PC_{100} was calculated from a graph of dose against resistance.

Results: Acute bronchoconstriction; The peak increase in lung resistance in the 15 minutes following antigen challenge is compared for treatment versus control studies.

Total cell count; The total cell count (cells per ml of BAL fluid) at 0 hours is subtracted from the total cell count at +24 hr, to give a value representing cell influx following antigen challenge. This value is compared for the treatment study versus the control study.

Total Eosinophils; From a cytospin preparation the percentage of eosinophils in the lavage fluid can be measured. From this value and the total cell count we calculate the total eosinophil count. As for total cells, the difference between the 24 hr count and the time 0 hour count gives a measure of the eosinophil influx, and this influx is compared for the treatment study versus the control study.

Airway Hyperresponsiveness; The values for the PC_{100} obtained at +24 hr, and 7 days (baseline) before the antigen challenge are converted into log_{10}. The baseline value is subtracted from the +24 hr value to give a log shift value. This log shift following the treatment study is compared to the log shift from the control study.

The same animals are used for both control and treatment studies, so they act as their own controls.

Sheep Model of Asthma

The allergic sheep model of asthma was also employed for the in vivo evaluation of the compounds of the invention as antiasthmatics. These methods have been published previously (see Abraham et al. (1983) Amdm. Rev. Respir. Dis. 128:839-844).

Each sheep serves as its own control. Body weights for these animals ranged from 20-50 kilograms. The treatments (vehicle or drug treatment) are administered prior to the antigen challenge, the route of administration and dosing regime will vary according to the type of compound being studied.

Twenty-four hours after antigen challenge in both the control and drug trial, the sheep developed airway hyper-responsiveness. Airway hyper-responsiveness is expressed as PC_{400}, the concentration of carbachol that causes a 400% increase in SRL; therefore, a decrease in PC_{400} indicates hyperresponsiveness.

Pharmacokinetics of Tryptase Inhibitors

So far known tryptase inhibitors (e.g. the preferred compound cis-1, 5-cyclooctylene bis[4-(4-guanidinobenzylcarbamoyl)-1-piperazinecarboxylate] in WO 9609297) showed a poor bioavailability in rat, dog and other species after oral administration. Therefore, these compounds had been inappropriate for an oral treatment.

The compounds of the invention surprisingly showed improved oral bioavailability in rats, dogs and primates.

Pharmacokinetic Investigations Rat and Dog and Monkey

Animal Experiment - Intravenous Administration			
Species	Rat	Dog	Monkey
Strain / race	Wistar	Beagle	Cynomolgus
Dose	1 mg/kg	1 mg/kg	2 mg/kg
Mode of administration	Bolus	1 min Infusion	0.5 min infusion
Formulation	PEG:Et:H_2O -5:1:4	PEG:Et:H_2O - 5:1:4	PEG:Et:H_2O-5:1:4
Volume	1 mg/kg	0.3 mg/kg	0.5 mg/kg
Blood Collection	Retroorbital Puncture, median aorta	Vena jugularis	Femoral vein
Time points	0.033 to 8 hours	0.033 to 8 hours	0.05 to 7 hours

PEG:Et:H_2O=Polyethylene glycol:Ethanol:Water

Animal Experiment - Oral Administration			
Species	Rat	Dog	Monkey
Strain / race	Wistar	Beagle	Cynomolgus
Dose	1 mg/kg	1 mg/kg	10 mg/kg
Mode of administration	Gavage	Gavage	Gavage
Formulation	PEG:Et:H_2O -5:1:4	PEG:Et:H_2O - 5:1:4	PEG:Et:H_2O-5:1:4
Volume	5 ml/kg	0.3 ml/kg	2.5 ml/kg
Blood Collection	Retroorbital Puncture, median aorta	Vena jugularis	Femoral vein
Time points	0.17 to 8 hours	0.17 to 24 hours	0.25 to 24 hours

Handling of Blood Samples

Blood was collected in heparinized syringes and cooled in ice water until centrifugation.

Plasma was frozen immediately after centrifugation and stored below -15°C until analysis.

Determination of Plasma Concentrations

To 0.1 ml plasma an internal standard was added. Plasma proteins were precipitated with acetonitrile and a sample was centrifuged at 14000 rpm for 10 min. The supernatant was withdrawn and evaporated to dryness under a gentle stream of nitrogen in a 40°C water bath. The residue was dissolved acetonitrile: ammonium acetate buffer 1:1.

Calibration samples: Known amounts of the compounds were added to plasma from untreated animals and the samples were treated in the same way. Plasma concentrations were determined via LC/MS with Turbo Ion Spray.

Tryptase Inhibitors - Bioavailability (%)			
	WO 9609297	present invention	
	example 3* in WO 9609297	example 1	example 6
- Rat	0.3 %	31 %	72 %
-Dog	0.2-7 %	57 %	74 %
- Monkey	n.d.	n.d.	100 %

n.d. = not determined; * cis-1,5-cyclooctylene bis [4-(4-guanidinobenzylcarbamoyl)-1-

piperazinecarboxylate] sulfate

Thus, the invention provides compounds and compositions that are useful for the prevention and treatment of immunomediated inflammatory disorders in mammals such as human, farm animal or domestic pet, in particular those associated with the respiratory tract, including asthma and allergic rhinitis.

The invention also relates to a method of treating a mammal such as a human, a farm animal, or a domestic pet, to achieve an effect, in which the effect is: prevention and treatment of diseases or pathological conditions including allergic conjunctivitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other athritic conditions, multiple sclerosis, interstitial cystitis, chronic obstructive pulmonary disease including chronic bronchitis and emphysema, skin diseases such as urticaria, allergic dermatitis, atopic dermatitis, bullous pemphigoid, psoriasis, and scleroderma; pulmonary fibrosis, interstitial pneumonia, nephritis, hepatic fibrosis, hepatitis, hepatic cirrhosis, Crohn's disease, ulcerative colitis, nasal allergy, peptic ulcers, gastric disease induced by non-steroidal inflammatory agents, cardiac infarction, disseminated intravascular coagulation, pancreatitis, multi organ failure, anaphylaxis, interstitial lung disease, gingivitis, periodontitis, cancer such as bladder and breast cancer, virus infections (e.g. Influenza virus, Sendai virus, human immunodefidiency virus, syncytial virus), ocular allergy (including atopic, vernal and giant papillary keratoconjunctivitis, contact blepharoconjunctivitis), inflammatory bowel disease, allergic contact dermatitis, emphysema, adult respiratory distress syndrome, bladder diseases, wound healing, bronchiectasis, pathological conditions associated with hyperplasia; angina, fibrotic diseases such as fibrotic lung disease, artherosclerosis, and cardiomyopathic disorders; diseases in which matrix metalloproteases are activated such as: chronic obstructive pulmonary disease including chronic bronchitis and emphysema; cystic fibrosis; bronchiectasis; adult respiratory distress syndrome (ARDS); allergic respiratory disease including allergic rhinitis; diseases linked to TNFα production including acute pulmonary fibrotic diseases, pulmonary sarcoidosis, silicosis, coal worker's pneumoconiosis and alveolar injury;

alleviation of osteoarthritis; alleviation of rheumatoid arthritis; alleviation of septic arthritis; alleviation of autoimmune disease; alleviation of autoimmune encephalomyelitis; alleviation of periodontal disease; alleviation of corneal ulceration; alleviation of proteinuria; alleviation of aneurysmal aortic disease; alleviation of dystrophobic epidermolysis bullosa; alleviation of diseases of abnormal bone loss including osteoporosis; alleviation of temporo

mandibular joint disease; alleviation of demyelinating diseases of the nervous system including multiple sclerosis; alleviation of chronic obstructive pulmonary disease; alleviation of acute and chronic neurodegenerative disorders including stroke, spinal cord and traumatic brain injury, amyotrophic lateral sclerosis, cerebral amyloid angiopathy, CNS injuries in AIDS, Parkinson's disease, Alzheimer's disease, Huntington's diseases, prion diseases, myasthenic gravis, and Duchenne's muscular dystrophy; alleviation of cardiovascular and pulmonary diseases including atherosclerosis, thrombotic events, atheroma, hemodynamic shock, unstable angina, restenosis, heart failure, and chronic obstructive pulmonary disease; alleviation of decubital ulcers; alleviation of aneurysmal diseases including those of the aorta, heart or brain; alleviation of metabolic diseases including diabetes and obesity mediated by insulin resistance, macular degeneration and diabetic retinopathy mediated by agiogenesis; alleviation of cachexia; alleviation of premature skin aging;

alleviation of diseases linked to TNFα production including acute rheumatic fever, bone resorption, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria and cerebral malaria, congestive heart failure, damage following heart disease, arteriosclerosis including atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, pancreatitis including systemic complications in acute pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies, host-versus-graft reactions including ischemia reperfusion injury, allograft rejections, complications due to total hip replacement, tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chagas' disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, the effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, Borrelia burgdorferi infections, Treponema pallidum infections, cytomegalovirus infections, Influenza virus infections, Sendai virus infections, Theiler's encephalomyelitis, and human immunodeficiency virus infections;

retardation of tumor metastasis; retardation of tumor growth or angiogenesis

associated with tumor growth; retardation of degenerative cartilage loss following traumatic joint injury; reduction of pain; reduction of coronary thrombosis from atherosclerotic plaque rupture; improved birth control; or improved wound repair including that due to burns;

the method comprising administering an amount of a compound of the invention as described above, and in more detail in the detailed description below, which is effective to inhibit the activity of at least one matrix metalloprotease, resulting in achievement of the desired effect.

The compositions containing the compounds of the invention can be administered for therapeutic and/or prophylactic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease, as described above, in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount or dose." Amounts effective for this use will depend on the severity and course of the disease, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

In prophylactic applications, the compositions containing the compounds of the invention are administered to a patient susceptible to or otherwise at risk of a particular disease in an amount sufficient to prevent or ameliorate the onset of symptoms. Such an amount is defined to be a "prophylactically effective amount of dose." These can be administered orally or by inhalation. In this use, the precise amounts again depend on the patient's state of health, weight, and the like.

Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved condition is retained. When the symptoms have been alleviated to the desired level, treatment can cease. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of the disease symptoms.

In general, a suitable effective dose of the compounds of the invention will be in the range of 0.05 to 1000 milligram (mg) per recipient per day, preferably in the range of 0.1 to 100 mg per day. The desired dosage is preferably presented in one, two, three, four or more subdoses administered at appropriate intervals throughout the day. These subdoses can be administered as unit dosage forms, for example, containing 0.01 to 1000 mg, preferably 0.01 to 100 mg of active

ingredient per unit dosage form.

The composition used in these therapies can be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms, such as tablets, enteric coated tablets, pills, powders, liquid solutions or suspensions, liposomes, injectable and infusible solutions. Inhalable preparations, such as aerosols, are also included. Preferred formulations are those directed to oral, intranasal, topical and parenteral applications, but it will be appreciated that the preferred form will depend on the particular therapeutic application at hand. Especially preferred formulations are oral or aerosol. The methods for the formulation and preparation of therapeutic compositions comprising the compounds of the invention are well known in the art and are described in, for example, REMINTON'S PHARMACEUTICAL SCIENSE AND THE MERCK INDEX 11th Ed., (Merck & Co. 1989).

Abbreviations:

EDC or WSCI HCI: N-(3-dimethylaminopropyl)-N' -ethylcarbodiimide hydrochloride

NMM: N-methylmorpholine

HOBt: 1-hydroxy-benzotriazole

DMPU: 1,3-dimethyltetrahydro-2(1H)-pyrimidone

PyBOP: benztriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

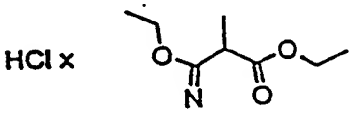
PyBroP: bromo-tris-pyrrolidinophosphonium hexafluorophoshate

DEAD: diethyl azodicarboxylate

Starting Compounds

Example 1A

2-Ethoxycarbonimidoylpropionic acid ethyl ester hydrochloride



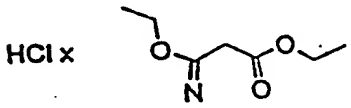
Ethyl 2-cyanopropionate (100g; 787mmol) was dissolved in toluene (350ml) and ethanol (71ml) and the solution was cooled to 0°C. Dry hydrogen chloride was passed through the solution at -5 - 0°C for 40min.. The mixture was allowed to warm to room temperature and stirred over night. Most of the solvent was evaporated in vacuo and after addition of diethyl ether / cyclohexane (1:1, 600ml) and cooling to 5°C the product was filtered off, washed with cyclohexane and dried in vacuo.

Yield: 151g (92% of theory), white solid

^{1}H-NMR (300 MHz, DMSO-d_6): 1.20 (t, 3H), 1.30 (m, 6H), 4.15 (m, 3H), 4.50 (q, 2H), 12.2 (br s, 2H)

Example 2A

2-Ethoxycarbonimidoylacetic acid ethyl ester hydrochloride

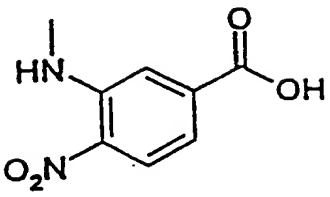


The preparation was carried out in analogy to the preparation of example 1A starting from ethyl cyanoacetate.

Yield: 73% of theory; white solid

Example 3A

3-Methylamino-4-nitrobenzoic acid



A solution of 3-methoxy-4-nitrobenzoic acid (500g; 2.536mol) in aqueous methylamine (40%, 2500ml) was heated in an autoclave at 100°C for 15h, allowed to cool to room temperature, and poured into a stirring slurry of 2N HCl and ice to give an orange precipitate. The precipitate was collected by filtration, rinsed with water and crystallized from hot ethanol to provide 3-methylamino-4-nitrobenzoic acid.

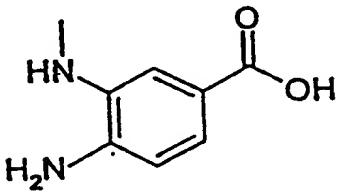
Yield: 448g (90% of theory) orange crystals.

^{1}H-NMR (200 MHz, DMSO-d_6): 2.99 (d, 3H, J=7 Hz), 7.15 (dd, 1H, J=9Hz and 1Hz), 7.48 (d, 1H, J=1Hz), 8.15 (d, 1H, J=9Hz), 8.21 (q, 1H, J=7 Hz), 13.55 (br s, 1H);

MS (DCI/NH_3) $C_8H_8N_2O_4$ m/e calc 196.2; found 214 ($M+NH_4^+$).

Example 4A

4-Amino-3-methylaminobenzoic acid



A solution of 3-methylamino-4-nitrobenzoic acid (example 3A) (50.0g; 255mmol) in THF (400ml) and methanol (150ml) was hydrogenated at 3bar in the presence of Palladium (10% on charcoal; 1.7g) for 15h. The reaction mixture was filtered through kieselgur and the filtrate was concentrated in vacuo. The residue was crystallized from dichloromethane to provide 4-amino-3-methylaminobenzoic acid.

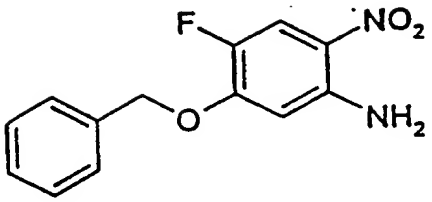
Yield: 40.3g (95% of theory) red-brown crystals

^{1}H-NMR (200 MHz, DMSO-d_6): 2.72 (s, 3H), 4.78 (br s, 1H), 5.29 (br s, 2H), 6.52 (d, 1H, J=9Hz), 7.14 (dd, 1H, J=9 and1 Hz), 11.9 (br s, 1H);

MS (DCI/NH_3) $C_8H_{10}N_2O_2$ m/e calc 166.2; found 167 ($M+H^+$).

Example 5A

5-Benzyloxy-4-fluoro-2-nitroaniline



To a solution of sodium *tert.*-butylate (14.35g; 149mmol) in THF (400ml) was added at 0°C bezylalcohol (24.84g; 230mmol). After stirring for 15min 4,5-difluoro-2-nitroaniline (20.0g; 115mmol) was added at 0 - 3°C. The reaction was allowed to warm to room temperature and stirred for 15h. After addition of ethyl acetate (500ml), the reaction mixture was washed with sat. aq. $NaHCO_3$ solution (2 x 150ml). The aqueous layer was extracted with ethyl acetate (2 x 150ml) and the combined organic layers were washed with brine (200ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was dissolved in dichloromethane and the product was precipitated with diethylether /cyclohexane, washed with diethylether/cyclohexane (1:10), collected by filtration and dried in vacuo.

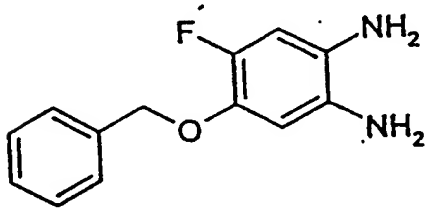
Yield: 23.6 g (78% of theory) light brown crystals

^{1}H-NMR (200 MHz, DMSO-d_6): 5.18 (s, 2H), 6.74 (d, 1H, J=8Hz), 7.30-7.55 (m, 5H), 7.55 (s, 2H), 7.79 (d, 1H, J=11 Hz);

MS (DCI/NH_3) $C_{13}H_{11}FN_2O_3$ m/e calc 262.2; found 280 ($M+NH_4^+$).

Example 6A

2-Amino-5-benzyloxy-4-fluoroaniline



To a solution of 5-benzyloxy-4-fluoro-2-nitroaniline (example 5A) (23.44; 89.4mmol) in ethyl acetate (1400ml) was added $SnCl_2x2H_2O$ (2100.8g; 447mmol). The reaction mixture was stirred at 70°C for 15h, cooled to room temperature followed by the addition of. sat. aq. $NaHCO_3$ solution (1000ml). Then solid $NaHCO_3$ (approx. 10g) was added until the color of the mixture turned from green to brown. The tin salts were removed by filtration through kieselgur. After separation of the layers, the aqueous phase was extracted with ethyl acetate (2 x 300ml) and the combined organic layers were washed with brine (1000ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in dichloromethane and the product was

precipitated with diethylether/hexane, washed with diethylether/hexane (1:10), collected by filtration and dried in vacuo.

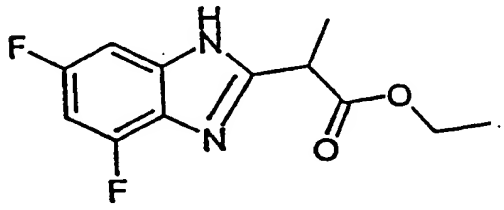
Yield: 17.21 g (83% of theory) light brown crystals

^{1}H-NMR (200 MHz, DMSO-d_6): 4.33 (br s, 4H), 4.93 (s, 2H), 6.36 (d, 1H, J=12Hz), 6.39 (d, 1H, J=8Hz), 7.25-7.45 (m, 5H);

MS (DCI/NH_3) $C_{13}H_{13}FN_2O$ m/e calc 232.3; found 233 ($M+H^+$).

Example 7A

Ethyl 2-(4,6-difluoro-1*H*-benzimidazol-2-yl)propionate



A mixture of example 1A (5.28g; 25.2mmol) and 2-amino-4,6-difluoroaniline (J. Med. Chem. 38, 1995, 4906; 3.03g; 21.0mmol) and ethanol (70ml) was heated to reflux for 3h. The solvent was evaporated in vacuo and the residue was taken up in ethyl acetate and washed twice with sat. aq. $NaHCO_3$ solution and with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by chromatography on silicagel (ethyl acetate:dichloromethane=1:2).

Yield: 4.27 g (80% of theory) tan crystals

^{1}H-NMR (200 MHz, DMSO-d_6): 1.18 (t, 3H, J=7Hz), 1.56 (t, 3H, J=7Hz), 4.00-4.25 (m, 3H), 7.05 (dt, 1H, J=10 and 1Hz), 7.21 (dd, 1H, J=10 and 1Hz), 12.9 (br s, 1H);

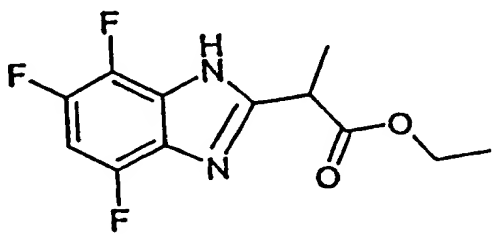
MS (DCI/NH_3) $C_{12}H_{12}F_2N_2O_2$ m/e calc 254.3; found 255 ($M+H^+$).

mp 132 °C;

Rf 0.81 (ethyl acetate/ dichloro methane = 3:2).

Example 8A

Ethyl 2-(4,6,7-trifluoro-1*H*-benzimidazol-2-yl)propionate



The preparation was carried out in analogy to example 7A starting from example 1A and 2-amino-3,4,6-trifluoroaniline (J. Fluorine Chem. 18, 1981, 507).

Yield: 70% of theory; tan crystals

^{1}H-NMR (200 MHz, DMSO-d_6): 1.18 (t, 3H, J=7Hz), 1.59 (t, 3H, J=7Hz), 4.02-4.22 (m, 3H), 7.35 (cm, 1H), 13.5 (br s, 1H);

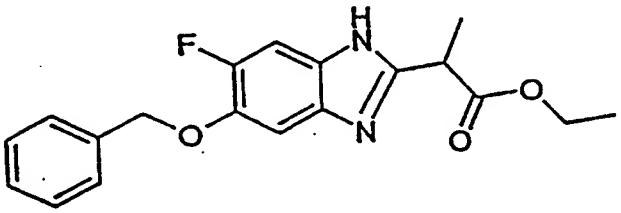
MS (DCI/NH_3) $C_{12}H_{11}F_3N_2O_2$ m/e calc 272.2; found 290 ($M+NH_4^+$).

mp 139 °C;

Rf 0.64 (ethyl acetate/ dichloro methane = 1:3).

Example 9A

Ethyl 2-(5-benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)propionate



The preparation was carried out in analogy to example 7A starting from example 1A and 2-amino-5-benzyloxy-4-fluoroaniline.

Yield: 76% of theory; oil

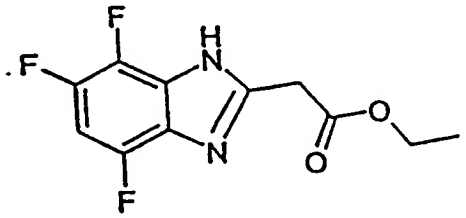
^{1}H-NMR (200 MHz, DMSO-d_6): 1.18 (t, 3H, J=7Hz), 1.52 (t, 3H, J=7Hz), 3.98-4.21 (m, 3H), 5.18 (s, 2H), 7.12-7.52(m, 7H), 12.4 (br s, 1H);

MS (DCI/NH_3) $C_{19}H_{19}FN_2O_3$ m/e calc 342.4; found 343 ($M+H^+$).

Rf 0.31 (cyclohexane/ ethyl acetate = 1:1).

Example 10A

Ethyl 2-(4,6,7-trifluoro-1*H*-benzimidazol-2-yl)acetate



The preparation was carried out in analogy to example 7A starting from example 2A and 2-amino-3,4,6-difluoroaniline.

Yield: 49% of theory; tan crystals

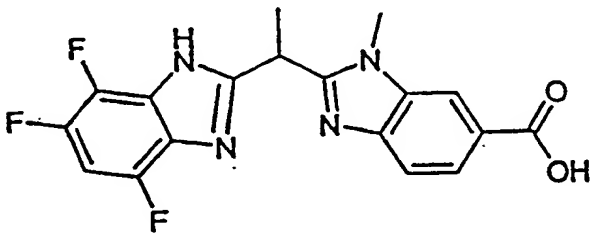
^{1}H-NMR (200 MHz, DMSO-d_6): 1.21 (t, 3H, J=7Hz), 4.01 (s, 2H), 4.17 (d, 2H, J=7Hz), 7.35 (cm, 1H), 13.5 (br s, 1H);

MS (DCI/NH_3) $C_{11}H_9F_3N_2O_2$ m/e calc 258.2; found 259 ($M+H^+$).

mp 168 °C.

Example 11A

2-[1-(4,6,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid



A mixture of ethyl 2-(4,6,7-trifluoro-1*H*-benzimidazol-2-yl)propionate (example 8A) (65.8g; 242mmol), example 4A (42.2g; 254mmol) and DMPU (1,3-dimethyltetrahydro-2(*1H*)-pyrimidone; 150ml) was stirred under vacuum at 50°C for 1h to remove residual gases and heated to 200°C (bath temperature) for 2h under argon in a distillation apparatus to remove the reaction water. The DMPU was evaporated in vacuo and the warm residue was dissolved in dichloromethane. After addition of water (500ml) the product crystallized and was collected by filtration. Further purification was achieved by heating a suspension of the crude product in refluxing dichloromethane/methanol (1:1, 1000ml) and filtration after cooling to room temperature, followed by heating of a product suspension in THF/methanol (1:1, 1000ml) and subsequent filtration. The product was dried in vacuo.

Yield: 60.0g (66% of theory); grey crystalline solid

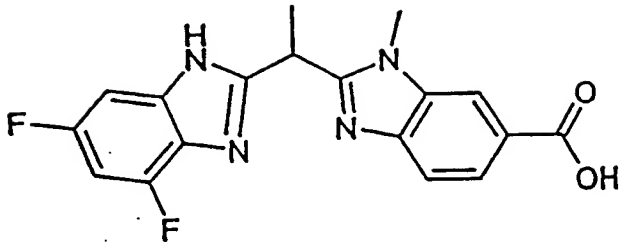
^{1}H-NMR (200 MHz, DMSO-d_6): 1.85 (t, 3H, J=7Hz), 3.84 (s, 3H), 5.01 (q, 1H, J=7Hz), 7.25-7.40 (m, 1H), 7.65 (d, 1H, J= 9Hz), 7.83 (dd, 1H, J=9 and 0,5Hz), 8.19 (d, 1H, J=0.5Hz), 13.1 (2 br s, 2H);

MS (DCI/NH_3) $C_{18}H_{13}F_3N_4O_2$ m/e calc 374.3; found 375 ($M+H^+$).

mp >250°C .

Example 12A

2-[1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid



The preparation was carried out in analogy to example 11A starting from ethyl 2-(4,6-difluoro-1*H*-benzimidazol-2-yl)propionate (example 7A) and example 4A.

Yield: 73% of theory); grey crystalline solid

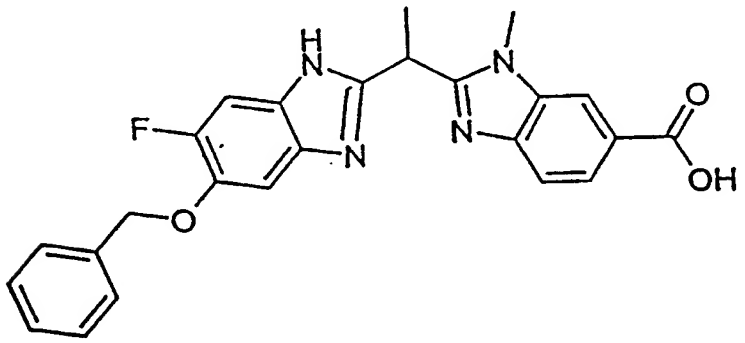
^{1}H-NMR (200 MHz, DMSO-d_6): 1.88 (t, 3H, J=7Hz), 3.83 (s, 3H), 5.00 (q, 1H, J=7Hz), 7.04 (dt, 1H, J=10 and 0.5Hz), 7.17 (dd, 1H, J=10 and 0.5Hz), 7.67 (d, 1H, J= 9Hz),.7.83 (dd, 1H, J=9 and 0,5Hz), 8.17 (d, 1H, J=0.5Hz), 12.9 (2 br s, 2H);

MS (DCI/NH_3) $C_{18}H_{14}F_2N_4O_2$ m/e calc 356.3; found 357 ($M+H^+$).

mp >330°C.

Example 13A

2-[1-(5-Benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid



The preparation was carried out in analogy to example 11A starting from ethyl 2-(5-benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)propionate (example 9A) and example 4A.

Yield: 65% of theory); foam

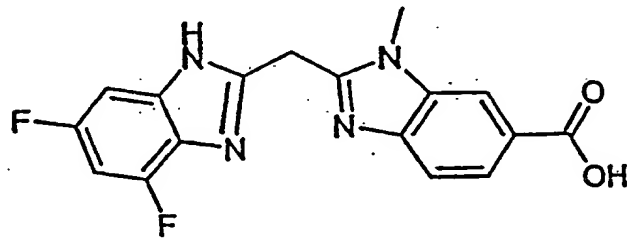
^{1}H-NMR (200 MHz, DMSO-d_6): 1.83 (t, 3H, J=7Hz), 3.79 (s, 3H), 4.90 (q, 1H, J=7Hz), 5.19 (s, 2H), 7.10-7.52 (m, 7H), 7.67 (d, 1H, J= 9Hz), 7.83 (dd, 1H, J=9 and 0,5Hz), 8.17 (d, 1H, J=0.5Hz), 12.4 and 12.8 (2 br s, 2H);

MS (DCI/NH_3) $C_{25}H_{21}FN_4O_3$ m/e calc 444.5 found 445 ($M+H^+$).

Rf 0.58 (dichloromethane/methanol = 6:1).

Example 14A

2-(4,6-difluoro-1*H*-benzimidazol-2-ylmethyl)-3-methyl-*3H*-benzimidazole-5-carboxylic acid



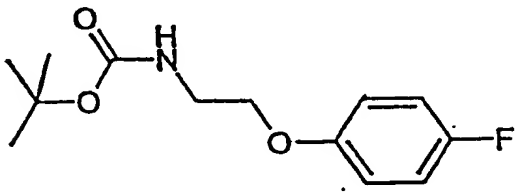
The preparation was carried out in analogy to example 11A starting from ethyl 2-(4,6-difluoro-1*H*-benzimidazol-2-yl)acetate and example 4A.

Yield: 92% of theory); grey crystalline solid

^{1}H-NMR (200 MHz, DMSO-d_6): 3.91 (s, 3H), 4.68 (s, 2H), 7.02 (dt, 1H, J=10Hz and 1Hz), 7.21 (dd, 1H, J=10Hz and 1Hz); 7.62 (d, 1H, J = 9Hz), 7.82 (dd, 1H, J=9 and 0.5Hz), 8.20 (d, 1H, J= 0.5 Hz); 12.8 and 12.9 (2 br s, 2H); MS(DCI/NH_3) $C_{17}H_{12}F_2N_4O_2$ m/e calc 342.3; found 343 ($M+H^+$), mp >250°C.

Example 15A

1-[(2-*N*-*tert*-butyloxycarbonylamino)ethoxy]-4-fluorobenzene



Cesium carbonate (61.1g; 187.4mmol) was added under argon to a solution of 4-fluorophenol (10.5g; 93.7mmol) in DMF (150ml). After stirring for 15min a solution of 1-bromo-2-(*N*-*tert*-butyloxycarbonylamino)ethane (J. Org. Chem. 53, 1988, 2226; 21.0g; 93.7mmol) in DMF (50ml) was added dropwise at room temperature and stirring was continued for 18h. Cesium carbonate was removed by filtration and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate (200ml) and water (300ml) and the water layer was extracted with ethyl acetate (2 x 100ml). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatograped over silicagel using toluene/ethyl acetate (10:1) as eluent.

Yield: 18.5g (77% of theory); oil

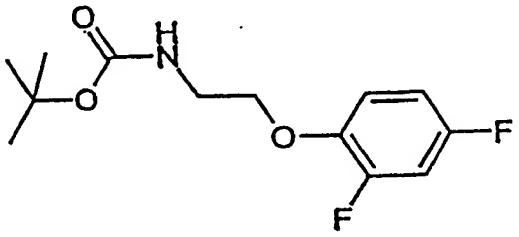
^{1}H-NMR (200 MHz, DMSO-d_6): 1.39 (s, 9H), 3.28 (dt, 2H, J=6 and 6Hz), 3.93 (t, 2H, J=6Hz), 6.91-7.15 (m, 5H);

MS (DCI/NH_3) $C_{13}H_{18}FNO_3$ m/e calc 255.3; found 256 ($M+H^+$);

R_f 0.44 (toluene/ethyl acetate = 10:1).

Example 16A

1-[(2-*N*-*tert*-butyloxycarbonylamino)ethoxy]-2,4-difluorobenzene



The preparation was carried out in analogy to example 15A starting from 2,4-difluorophenol.

Yield: (78% of theory); oil

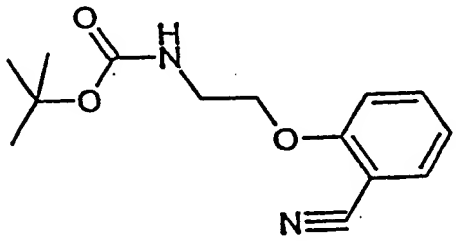
^{1}H-NMR (200 MHz, DMSO-d_6): 1.40 (s, 9H), 3.29 (dt, 2H, J=6 and 6Hz), 4.01 (t, 2H, J=6Hz), 6.95-7.36 (m, 4H);

MS (DCI/NH_3) $C_{13}H_{17}F_2NO_3$ m/e calc 273.3; found 274 ($M+H^+$);

R_f 0.42 (toluene/ethyl acetate = 10:1).

Example 17A

2-[(2-*N*-*tert*-butyloxycarbonylamino)ethoxy]benzonitrile



The preparation was carried out in analogy to example 15A starting from 2-cyanophenol.

Yield: (58% of theory); white solid

^{1}H-NMR (200 MHz, DMSO-d_6): 1.40 (s, 9H), 3.34 (dt, 2H, J=6 and 6Hz), 4.16 (t, 2H, J=6Hz), 7.05 (t, 1H, J=6Hz), 7.10 (t, 1H, J=8Hz), 7.28 (d, 1H, J=8Hz) 7.58-7.75(m, 2H);

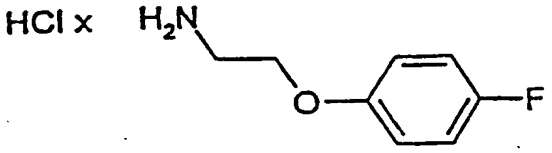
MS (DCI/NH_3) $C_{14}H_{18}N_2O_3$ m/e calc 262.3; found 280 ($M+NH_4^+$);

m.p.: 75-76°C

R_f 0.44 (toluene/ethyl acetate = 20:1).

Example 18A

1-(2-Aminoethoxy)-4-fluorobenzene hydrochloride



To a stirred solution of 1-[(2-*N*-*tert*-butyloxycarbonylamino)ethoxy]-4-fluorobenzene (20.3g; 79.3mmol) in 1,4-dioxane (50ml) was added at room temperature under argon 4N HCl in 1,4-dioxane (300ml). After stirring for 15h, precipitated product was collected by filtration, washed with diethyl ether and dried in vacuo.

Yield: 12.3g (80% of theory); white crystalline solid

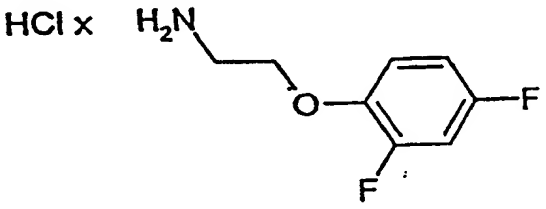
^{1}H-NMR (200 MHz, DMSO-d_6): 3.18 (t, 2H, J=6 Hz), 4.15 (t, 2H, J=6Hz), 6.95-7.22 (m, 4H), 8.28 (s, 3H);

MS (DCI/NH_3) $C_8H_{11}ClFNO$ m/e calc 155.1 x 36.5; found 156 ($M+H^+$);

m.p.: >200°C

Example 19A

1-(2-Aminoethoxy)-2,4-difluorobenzene hydrochloride



The preparation was carried out in analogy to example 18A starting from 1-[(2-*N*-*tert*-butyloxycarbonylamino)ethoxy]-2,4-difluorobenzene

Yield: 88% of theory; white crystalline solid

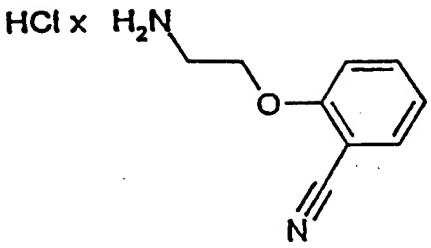
^{1}H-NMR (200 MHz, DMSO-d_6): 3.20 (t, 2H, J=6 Hz), 4.28 (t, 2H, J=6Hz), 7.00-7.40 (m, 3H), 8.42 (s, 3H);

MS (DCI/NH_3) $C_8H_{10}ClFNO$ m/e calc 173.2 x 36.5; found 174 ($M+H^+$);

m.p.: 220-223°C

Example 20A

2-(2-Aminoethoxy)benzonitrile hydrochloride



The preparation was carried out in analogy to example 18A starting from 2-[(2-*N*-*tert*-butyloxycarbonylamino)ethoxy]benzonitrile (example 17A).

Yield: 92% of theory; white crystalline solid

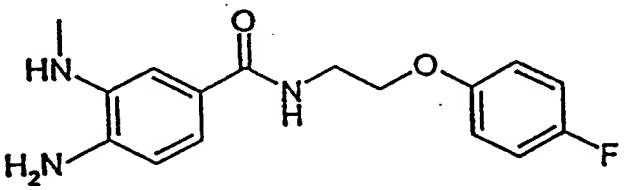
^{1}H-NMR (200 MHz, DMSO-d_6): 3.25 (t, 2H, J=6 Hz), 4.38 (t, 2H, J=6Hz), 7.17 (t, 1H, J=7Hz), 7.31 (d, 2H, J=7Hz) 7.63-7.82 (m, 2H,), 8.28 (s, 3H);

MS (DCI/NH_3) $C_9H_{11}ClN_2O$ m/e calc 162.2 x 36.5; found 180 ($M+NH_4^+$);

m.p.: 183°C

Example 21A

4-Amino-*N*-[2-(4-fluorophenoxy)ethyl]-3-methylaminobenzamide



To a solution of 4-amino-3-methylaminobenzoic acid (2.05g; 12.3mmol) in DMF (120ml) was added under Argon at -5°C PyBOP (benztriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; 7.69g; 14.8mmol) and 1-hydroxybenzotriazole (2.16g; 16.0mmol). After stirring for 15min *N*-methylmorpholine (4.98g; 49.3mmol) and 1-(2-aminoethoxy)-4-fluorobenzene hydrochloride (example 18A) (2.36g; 12.3mmol) were subsequently added at -5°C - 0°C. After stirring for 18h at room temperature water (1000ml) was added and the mixture was extracted with ethyl acetate (3 x 400ml). The combined organic layers were washed with brine (1000ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatograped over silicagel using toluene/ethyl acetate (1:1) as eluent.

Yield: 2.1g (56% of theory); foam

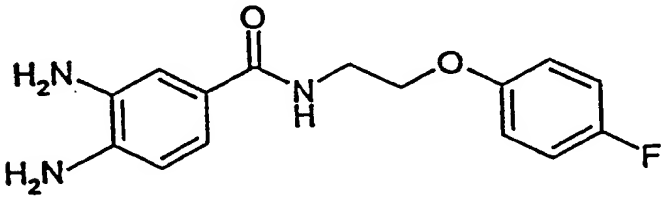
^{1}H-NMR (400 MHz, DMSO-d_6): 2.75 (s, 3H), 3.57 (dt, 2H, J=6 and 6Hz), 4.04 (t, 2H, J=6Hz), 4.69 (s, 1H), 4.97 (s, 2H), 6.51 (d, 1H, J=8Hz), 6.91 (d, 1H, J=0.5Hz), 6.95-7.15 (m, 5H), 8.18 (t, 1H, J=6Hz);

MS (DCI/NH_3) $C_{16}H_{18}FN_3O_2$ m/e calc 303.3; found 304 ($M+H^+$);

R_f 0.50 (ethyl acetate).

Example 22A

3,4-Diamino-*N*-[2-(4-fluorophenoxy)ethyl]benzamide



The preparation was carried out in analogy to example 21A starting from 3,4-diamino benzoic acid and 1-(2-aminoethoxy)-4-fluorobenzene hydrochloride (example 18A)

Yield: 47% of theory; oil

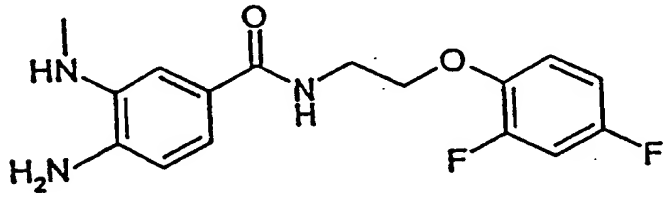
^{1}H-NMR (200 MHz, DMSO-d_6): 3.55 (dt, 2H, J=6 and 6Hz), 4.04 (t, 2H, J=6Hz), 4.60 (s, 2H), 4.97 (s, 2H), 6.48 (d, 1H, J=8Hz), 6.92-7.18 (m, 6H), 8.10 (t, 1H, J=6Hz);

MS (DCI/NH_3) $C_{15}H_{16}FN_3O_2$ m/e calc 289.3; found 290 ($M+H^+$);

R_f 0.32 (dichloromethane/ ethanol = 20:1.5).

Example 23A

4-Amino-*N*-[2-(2,4-difluorophenoxy)ethyl]-3-methylaminobenzamide



The preparation was carried out in analogy to example 21A starting from 4-amino-3-methylaminobenzoic acid and 1-(2-aminoethoxy)-2,4-difluorobenzene hydrochloride (example 19A).

Yield: 60% of theory; oil

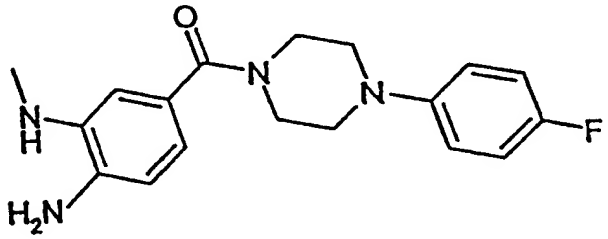
^{1}H-NMR (200 MHz, DMSO-d_6): 2.77 (s, 3H), 3.58 (dt, 2H, J=6 and 6Hz), 4.14 (t, 2H, J=6Hz), 4.69 (s, 1H), 5.01 (s, 2H), 6.51 (d, 1H, J=8Hz), 6.92 (d, 1H, J=0.5Hz), 6.98-7.30 (m, 4H), 8.20 (t, 1H, J=6Hz);

MS (DCI/NH_3) $C_{15}H_{17}F_2N_3O_2$ m/e calc 321.3; found 322 ($M+H^+$);

R_f 0.52 (ethyl acetate).

Example 24A

4-[(4-fluorophenyl)piperazin-1-ylcarbonyl]-2-methylaminoaniline



The preparation was carried out in analogy to example 21A starting from 4-amino-3-methylaminobenzoic acid and 4-(4-fluorophenyl)piperazine

Yield: 67% of theory; brown solid

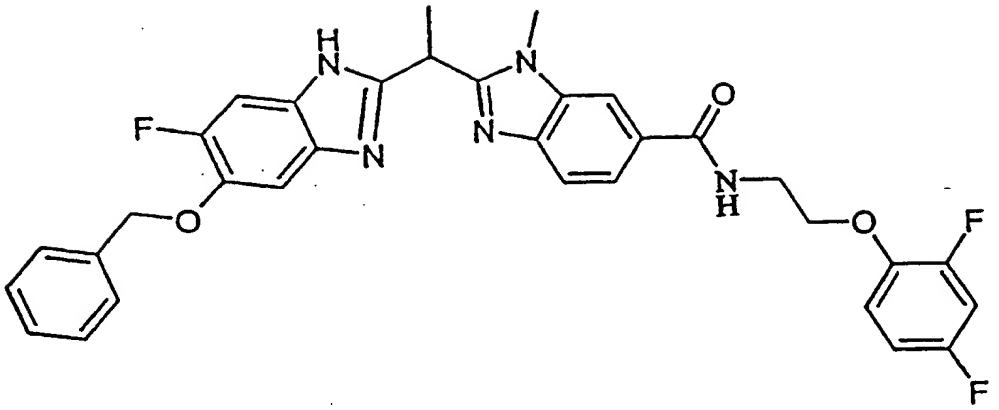
^{1}H-NMR (400 MHz, DMSO-d_6): 2.71 (s, 3H), 3.09 (cm, 4H), 3.61 (cm, 4H), 4.78 (s, 1H), 4.92 (s, 2H), 6.41-6.60 (m, 3H) 6.92-7.14 (m, 4H);

MS (DCI/NH_3) $C_{18}H_{21}FN_4O_2$ m/e calc 328.4; found 329 ($M+H^+$);

R_f 0.27 (ethyl acetate).

Example 25A

2-[1-(5-Benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)ethyl]-5-[*N*-2-(2,4-difluorophenyl-1-oxy)ethylaminocarbonyl]-3-methyl-3*H*-benzimidazole



To a solution of 2-[1-(5-benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid (example 13A) (1.11g; 2.50mmol) and 1-(2-aminoethoxy)-2,4-difluorobenzene hydrochloride (example 19A) (0.52g, 2.50mmol) and N-methylmorpholine (0.32g; 3.13mmol) in DMF (30ml) was added under Argon at 0°C 1-hydroxybenzotriazole (0.44; 3.25mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.53g; 2.75mmol). After stirring for 18h at room temperature the solvent was evaporated in vacuo, water (60ml) was added and the mixture was extracted with ethyl acetate (3 x 60ml). The combined organic layers were washed with water (50ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatograped over silicagel using dichloromethane/ethanol (20:1) as eluent.

Yield: 1.01g (68% of theory); tan crystalline solid

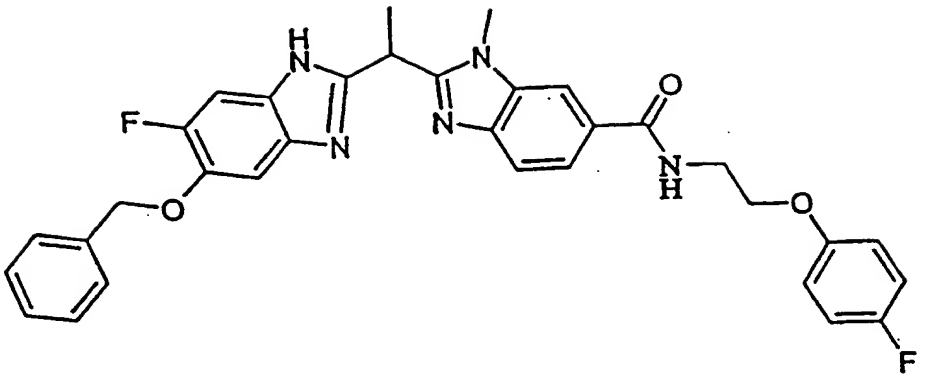
^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (t, 3H, J=7Hz), 3.68 (dt, 2H, J=6 and 6Hz), 3.77 (s, 3H), 4.20 (t, 2H, J=6Hz), 4.90 (q, 1H, J=7Hz), 5.18 (s, 2H), 6.95-7.52 (m, 10H), 7.64 (d, 1H, J=8Hz), 7.75 (dd, 1H, J=8 and 0.5Hz), 8.10 (d, 1H, J=0.5Hz), 8.71 (t, 1H, J=6Hz), 12.4 (br s, 1H);

MS (DCI/NH_3) $C_{33}H_{28}F_3N_5O_3$ m/e calc 599.6; found 600 ($M+H^+$);

R_f 0.24 (dichloromethane/ethanol (20:1)).

Example 26A

2-[1-(5-Benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)ethyl]-5-[*N*-2-(4-fluorophenyl-1-oxy)ethylaminocarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 25A starting from 2-[1-(5-benzyloxy-6-fluoro-*1H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid (example 13A) and 1-(2-aminoethoxy)-4-fluorobenzene hydrochloride (example 18A).

Yield: 84% of theory; foam

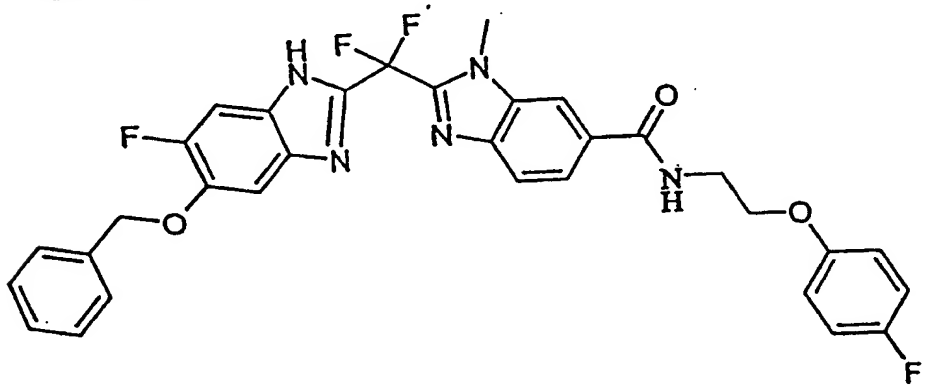
^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (t, 3H, J=7Hz), 3.68 (dt, 2H, J=6 and 6Hz), 3.78 (s, 3H), 4.15 (t, 2H, J=6Hz), 4.91 (q, 1H, J=7Hz), 5.18 (s, 2H), 6.95-7.52 (m, 11H), 7.65 (d, 1H, J=8Hz), 7.75 (dd, 1H, J=8 and 0.5Hz), 8.10 (d, 1H, J=0.5Hz), 8.71 (t, 1H, J=6Hz), 12.4 (br s, 1H);

MS (DCI/NH_3) $C_{33}H_{29}F_2N_5O_3$ m/e calc 581.6; found 582 ($M+H^+$);

R_f 0.10 (dichloromethane/methanol (30:1)).

Example 27A

2-[(5-Benzyloxy-6-fluoro-1*H*-benzimidazol-2-yl)difluoromethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxamide.

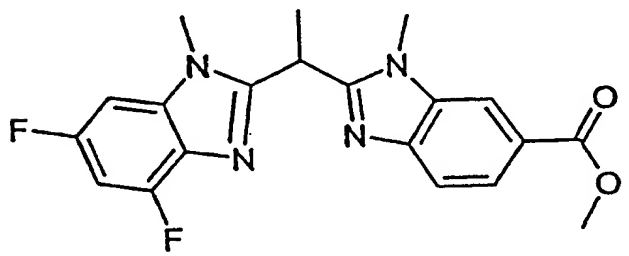


A solution of difluoromalonic acid (J. Fluorine Chem. 49, 1990, 275; 1.61g; 9.19mmol) and 4-amino-3-methylamino benzoic acid N-2-(4-fluorophenoxy)ethylamide (3.10g; 9.19mmol) in

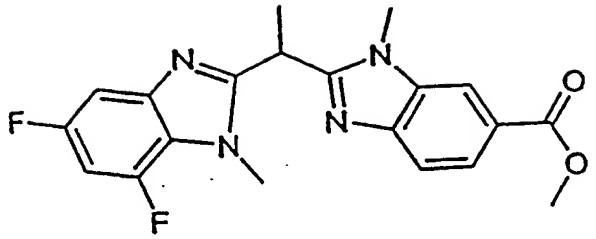
DMF (40ml) was stirred under argon at -10°C for 10 min. PyBroP (bromo.tris-pyrrolidinophosphonium hexafluorophoshate; 4.58g; 9.83mmol) was slowly added to the solution at -10°C in portions over 5 min followed by N-methylmorpholine (2.79g; 27.6mmol). The mixture was allowed to warm to room temperature and stirring was continued for 3h. After cooling to -10°C PyBroP (4.58; 9.83 mmol) and then N-methylmorpholine (2.79g; 27.6mmol) and 2-amino-5-benzyloxy-4-fluoroaniline (2.13g; 9.19mmol) were slowly added. The mixture was allowed to warm to room temperature and stirring was continued for 18h. The mixture was poured into ice-water (500ml) and extracted with diethylether/ethyl acetate (3:1 / 3 x 150ml). The combined organic layers were washed with brine (2000ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was taken into acetic acid (40ml) and heated to 85°C under argon for 3h. The acetic acid was evaporated in vacuo and the residue was taken into sat. aq. $NaHCO_3$ solution (200ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatograped twice over silicagel using dichloromethane/ethanol (20:1 and 40:1) as eluent.
Yield: 1.19g (21% of theory); tan crystalline solid
^{1}H-NMR (200 MHz, DMSO-d_6): 3.68 (dt, 2H, J=6 and 6Hz), 3.96 (s, 3H), 4.14 (t, 2H, J=6Hz), 5.23 (s, 2H), 6.95-7.18 (m, 4H), 7.29-7.26 (m, 7H), 7.78-7.90 (m, 2H), 8.30 (s, 1H), 8.81 (t, 1H, J=6Hz), 13.7 (br s, 1H);
MS (ESI) $C_{32}H_{25}F_4N_5O_3$ m/e calc 603.6; found 604 ($M+H^+$);
R_f 0.67 (dichloromethane/methanol (10:1)).

Examples 28A and 29A

Example 28 A: Methyl 2-[1-(4,6-difluoro-1-methyl-1H-benzimidazol-2-yl)ethyl]-3-methyl-3H-benzimidazole-5-carboxylate



Example 29 A: Methyl 2-[1-(4,6-difluoro-3-methyl-3H-benzimidazol-2-yl)ethyl]-3-methyl-3H-benzimidazole-5-carboxylate



2-[1-(4,6-difluoro-1H-benzimidazol-2-yl)ethyl]-3-methyl-3H-benzimidazole-5-carboxylic acid (625mg; 1.754mmol) and methyliodide (747mg; 5.26mmol) were dissolved in DMF (10ml). Cesium carbonate (1.71g; 5.26mmol) was added and the mixture was stirred at room temperature for 15h. The DMF was evaporated in vacuo, the residue was taken up in water (20ml) and extracted with ethyl acetate (4 x 20ml). The combined organic layers were washed with brine (20ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatograped over silicagel using dichloromethane/ethanol (20:1) as eluent to provide an approx. 2:1 mixture of methyl 2-[1-(4,6-difluoro-1-methyl-1H-benzimidazol-2-yl)ethyl]-3-methyl-3H-benzimidazole-5-carboxylate and methyl 2-[1-(4,6-difluoro-3-methyl-3H-benzimidazol-2-yl)ethyl]-3-methyl-3H-benzimidazole-5-carboxylate (0.47). The regioisomers were separated using preparative HPLC (Kromasil 100 C18 5 µM, 250 x 20 mm, flow 25ml/min, T=50°C, detection 220nm)

Example 28A:

Yield: 202mg (30% of theory); white crystalline solid

^{1}H-NMR (400 MHz, DMSO-d_6): 1.82 (t, 3H, J=7Hz), 3.62 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 5.15 (q, 1H, J=7Hz), 7.07 (dt, 1H, J=9 and 1Hz), 7.38 (dd, 1H, J= 9 and 1Hz), 7.67 (d, 1H, J=9Hz), 7.82 (dd, 1H, J=9 and 0,5Hz), 8.18 (d, 1H, J=0.5Hz);

MS (ESI) $C_{20}H_{18}F_2N_4O_2$ m/e calc 384.4; found 385 ($M+H^+$).

HPLC retention time: 4.63 min

Example 29A:

Yield: 128mg (19% of theory); white crystalline solid

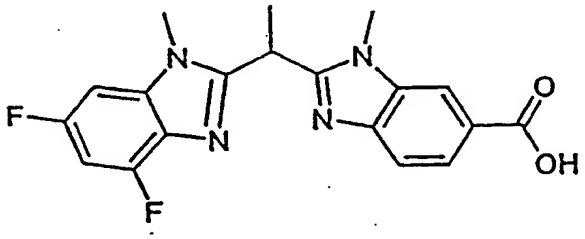
^{1}H-NMR (400 MHz, DMSO-d_6): 1.82 (t, 3H, J=7Hz), 3.77 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 5.18 (q, 1H, J=7Hz), 7.14 (dt, 1H, J=9 and 1Hz), 7.30 (dd, 1H, J= 9 and 1Hz), 7.68 (d, 1H, J=9Hz), 7.82 (dd, 1H, J=9 and 0,5Hz), 8.18 (d, 1H, J=0.5Hz);

MS (ESI) $C_{20}H_{18}F_2N_4O_2$ m/e calc 384.4; found 385 ($M+H^+$).

HPLC retention time: 6.15 min

Examples 30A

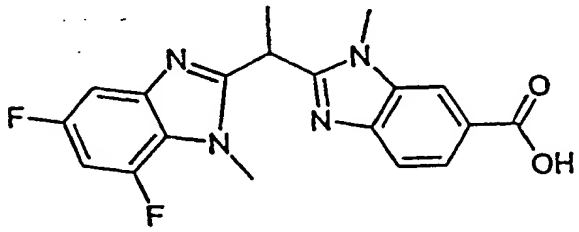
2-[1-(4,6-difluoro-1-methyl-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid



To a solution of methyl 2-[1-(4,6-difluoro-1-methyl-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylate (202mg; 0.526mmol) in THF (10ml) and methanol (40ml) was added 2N NaOH (5ml) and the mixture was stirred for 15h at room temperature. The solvents were evaporated in vacuo, the residue was taken up in water (5ml) and 1N HCl was added to adjust pH 4. Precipitated product was collected by filtration and dried in vacuo.
Yield: 126mg (65% of theory); white crystalline solid
^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (t, 3H, J=7Hz), 3.68 (s, 3H), 3.80 (s, 3H), 5.17 (q, 1H, J=7Hz), 7.08 (dt, 1H, J=9 and 1Hz), 7.40 (dd, 1H, J= 9 and 1Hz), 7.65 (d, 1H, J=9Hz), 7.82 (dd, 1H, J=9 and 0,5Hz), 8.18 (d, 1H, J=0.5Hz), 12.7 (br s, 1H);
MS (ESI) $C_{19}H_{16}F_2N_4O_2$ m/e calc 370.4; found 385 ($M-H^+$).

Examples 31A

2-[1-(4,6-difluoro-3-methyl-3*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylic acid



The preparation was carried out in analogy to example 30A starting from methyl 2-[1-(4,6-difluoro-3-methyl-3*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxylate

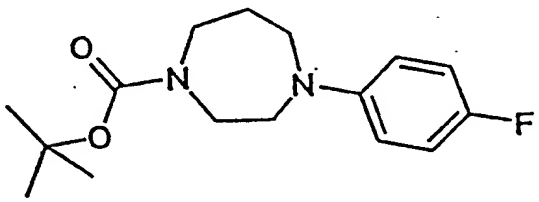
Yield: 74% of theory; white crystalline solid

^{1}H-NMR (400 MHz, DMSO-d_6): 1.82 (t, 3H, J=7Hz), 3.77 (s, 3H), 3.82 (s, 3H), 5.18 (q, 1H, J=7Hz), 7.15 (dt, 1H, J=9 and 1Hz), 7.32 (dd, 1H, J= 9 and 1Hz), 7.65 (d, 1H, J=9Hz), 7.82 (dd, 1H, J=9 and 0,5Hz), 8.18 (d, 1H, J=0.5Hz),12.8 (br s, 1H);

MS (ESI) $C_{19}H_{16}F_2N_4O_2$ m/e calc 370.4; found 385 ($M-H^+$).

Example 32A

1-(*N-tert.*-Butyloxycarbonyl)-4-(4-fluorophenyl)-1,4-diaza-cycloheptane



Tri-(*o*-tolyl)phosphine (0.11g; 0.36mmol) was added at room temperature under argon to a stirred suspension of tris-(dibenzylidenacetone)-dipalladium(0) (0.33g; 0.36mmol) in toluene (50ml). After addition of sodium tert.-butylate (1.16g; 12.1mmol), 4-bromo-1-fluorobenzene (1.51g; 8.61mmol) and 1-(*N-tert.*-Butyloxycarbonyl)-1,4-diaza-cycloheptane (2.00g; 9.99mmol) the mixture was stirred at 100°C under argon for 15h. The solution was decanted to remove palladium residues, washed with brine (2 x 30ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatograped over silicagel using dichloromethane/methanol (100:1) as eluent.

Yield: 0.49g (19% of theory);

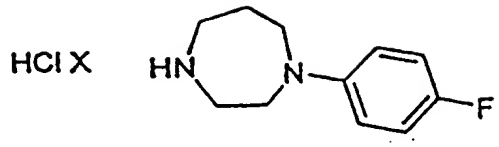
^{1}H-NMR (200 MHz, DMSO-d_6): 1.19 and 1.31 (2s, 9H, cis/trans amide bond isomers), 1.71-1.88 (m, 2H), 3.12-3.26 (m, 2H), 3.41-3.60 (m, 6H), 6.70 (cm, 2H), 6.96 (cm, 2H);

MS (ESI) $C_{16}H_{23}FN_2O_2$ m/e calc 294.4; found 295 ($M+H^+$);

R_f 0.67 (dichloromethane/methanol (10:1)).

Example 33A

1-(4-fluorophenyl)-1,4-diazacycloheptane



To a solution of 1-(*N-tert.*-butyloxycarbonyl)-4-(4-fluorophenyl)-1,4-diazacycloheptane (0.41g; 1.393mmol) in 1,4-dioxane (4.1ml) was added 4N HCl in 1,4-dioxane (8.2ml) and the mixture was stirred at room temperature for 2h. The solvent was evaporated in vacuo and the residue was treated with diethyl ether. The precipitated product was collected by filtration, washed with diethyl ether and dried in vacuo.

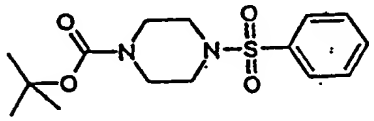
Yield: 0.30g (93% of theory);

^{1}H-NMR (200 MHz, DMSO-d_6): 2.00-2.21 (m, 2H), 3.02-3.28 (m, 4H), 3.47 (t, 2H, J=7Hz), 3.68 (cm, 2H), 6.76 (cm, 2H), 7.05 (cm, 2H), 9.05 (br s, 2H);

MS (EI) $C_{11}H_{16}ClFN_2$ m/e calc 194.2 x 36.5; found 194 (M^+).

Example 34A

4-Benzenesulfonyl-1-*tert*-butyloxycarbonylpiperazine



Triethylamine(0.56 mL, 4.02 mmol) was added to a solution of *tert*-butyloxypiperazine (500 mg, 2.68 mmol) in 3 mL of dichloromethane, then it was cooled to 0 °C. Benzenesulfonylchloride (0.39 mL, 3.22 mmol) was added to the solution and stirred for 3 hours. The solvent was evaporated in vacuo and the residue was washed with ether. The resulting white solid was filtrated and dried.

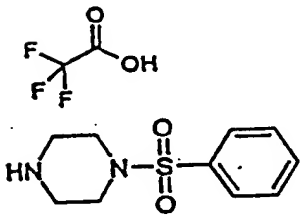
Yield : 860 mg (98.1% of theory), colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.34 (s, 9H), 2.85 (t, 4H, J=5.0 Hz), 3.39 (m, 4H), 7.63-7.68 (m, 2H), 7.72-7.75 (m, 3H);

Rf 0.66 (ethyl acetate / n-hexane = 1/1).

Example 35A

4-Benzenesulfonylpiperazine trifluoroacetate



To a solution of 4-benzenesulfonyl-1-*tert*-butyloxycarbonylpiperazine(860 mg, 2.64 mmol) in 10 mL of dichloromethane was added trifluoroacetic acid (0.24 mL, 3.16 mmol) at 0 °C. The solution was stirred for 1 hour at 0 °C and evaporated in vacuo. Ether was added to the residue to give a white solid.

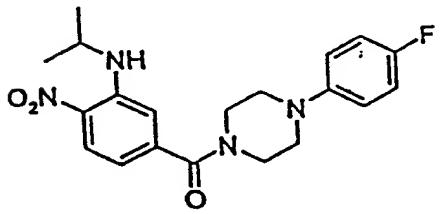
Yield : 740 mg (82.5% of theory), colorless powder;

^{1}H-NMR (300 MHz, DMSO-d_6) 3.09-3.12 (m, 4H), 3.18-3.22 (m, 4H), 7.70-7.73 (m, 2H), 7.77-7.80 (m, 2H), 8.76(br s, 2H);

MS (FAB) $C_{10}H_{14}N_2O_2S$ m/e calc 226; found 227 (MH^+).

Example 36A

1-[(4-Fluorophenyl)piperazin-1-yl]carbonyl-3-isopropylamino-4-nitrobenzene



In a sealed reaction vessel, a mixture of 3-methoxy-4-nitrobenzoic acid (2.72 g, 13.8 mmol), isopropylamine (4.0 mL) and water (7.0 mL) was stirred at 100 °C for 5 days. After cooled to room temperature, the reaction mixture was dissolved in cold water to afford an orange solution. Concentrated hydrochloric acid was added into the solution under an ice-water cooling until a light orange precipitate was no longer formed. The solid was collected by filtration, washed with water and dried to yield approximately 1 to 1 mixtures of 3-isopropylamino-4-nitrobenzoic acid hydrochloride and 3-methoxy-4-nitrobenzoic acid (2.19 g). To a solution of the mixture (2.19 g), 1-(4-fluorophenyl)piperazine (2.72 g, 15.1 mmol), triethylamine (3.51 mL, 25.2 mmol) and 1-hydroxybenzotriazole in *N,N*-dimethylformamide (80 mL) was added water-soluble carbodiimide hydrochloride (3.22 g, 16.8 mmol) in an ice-

water bath. The reaction mixture was stirred at 0 °C for 30 minutes, then, the ice-water bath was removed. After the mixture was stirred at room temperature for 17 hours, the mixture was diluted with ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with ethyl acetate (twice), and the combined organic layer was washed with brine. After dryness, silica gel column chromatography (n-hexane/ethyl acetate = from 2/1 to 1/1 as eluent) yielded 1.73 g of a brilliant orange solid. Yield 33% from 3-methoxy-4nitrobenzoic acid.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.34 (d, 6H, J=6.4 Hz), 3.04-3.18 (m, 4H), 3.56 (br s, 2H), 3.81-3.93 (m, 3H), 6.59 (dd, 1H, J=8.7, 1.7 Hz), 6.86-7.03 (m, 5H), 8.05 (d, 1H, J=7.1Hz), 8.22 (d, 1H, J=8.7 Hz);

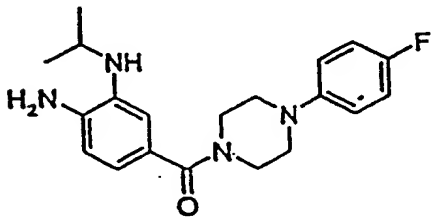
MS (FAB) $C_{20}H_{23}FN_4O_3$ m/e calc 386.4; found 387 (MH^+);

mp 201.6-202.7 °C;

Rf = 0.2 (n-hexane/ethyl acetate = 3/2).

Example 37A

4-Amino-1-[(4-fluorophenyl)piperazin-1-yl]carbonyl-3-isopropylaminobenzene



1-[(4-Fluorophenyl)piperazin-1-yl]carbonyl-3-isopropylamino-4-nitrobenzene (1.50 g, 3.88 mmol) was dissolved in methanol (80 mL), into a 100 mL reaction vessel of ISHII Catalytic Hydrogenator. 10%-Pd/C (0.20 g) was carefully added into the solution. After several times substitution of air to hydrogen, the reaction mixture was stirred at room temperature under 3 atoms of hydrogen until no more hydrogen was consumed, taking 4 hours. The reaction solution was filtrated through a thin layer of celite to remove Pd/C, and washed with methanol. The organic layer was concentrated *in vacuo* to afford 1.43 g of a light purple solid. Quantitative yield.

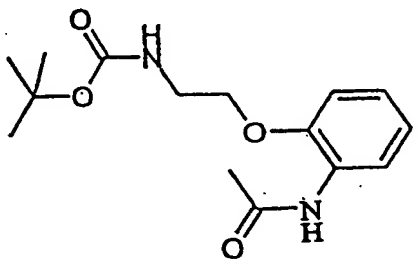
^{1}H-NMR (300 MHz, DMSO-d_6): 1.16 (d, 6H, J=6.3 Hz), 3.06-3.09 (m, 4H), 3.51-3.65 (m, 5H), 4.28 (d, 1H, J=7.4 Hz), 4.94 (s, 2H), 6.49-6.55 (m, 3H), 6.95-7.09 (m, 4H);

MS (FAB) $C_{20}H_{25}FN_4O$ m/e calc 356.4; found 357 (MH^+);

mp 63.6-67.5 °C.

Example 38A

N-Acetyl-2-[(2-*N*-*tert*.-butyloxycarbonylamino)ethoxy]aniline



The preparation was carried out in analogy to example 15A starting from 2-N-acetylaminophenol.

Yield: 3.0 g (76.1%.of theory), colorless oil

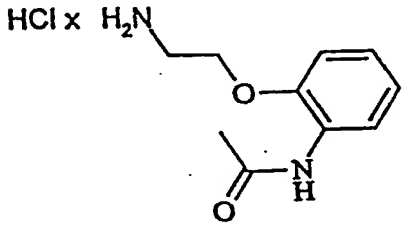
^{1}H-NMR (300 MHz, DMSO-*d6*): 1.40 (s, 9H), 2.13 (s, 3H), 3.34-3.40 (m, 2H), 3.97 (t, 2H, J=5.1 Hz), 6.80-7.00 (m, 4H), 7.16 (t, 1H, J=5.6 Hz), 8.89(s, 1H);

MS (FAB) $C_{15}H_{22}N_2O_4$ m/e calc 294.4; found 295 (MH^+);

Rf 0.30 (chloroform / ethyl acetate = 5/1).

Example 39A

N-Acetyl-2-(2-aminoethoxy)aniline hydrochloride



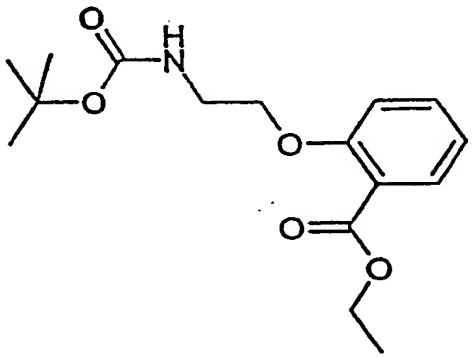
The preparation was carried out in analogy to example 18A starting from *N*-acetyl-2-[(2-*N*-*tert*.-butyloxycarbonylamino)ethoxy]aniline.

Yield: 0.8 g (34.0% of theory), colorless powder

^{1}H-NMR (300 MHz, DMSO-*d6*): 2.19 (s,3H), 3.23-3.28 (m, 2H), 4.19 (t, 2H, J=4.8 Hz), 6.88-6.90 (m, 1H), 6.99-7.34 (m, 2H), 7.31-7.34 (m, 1H) 8.49 (br s, 2H), 9.42 (s, 1H); MS (FAB) $C_{10}H_{14}N_2O_2$ m/e calc 194.2; found 195 (MH^+).

Example 40A

Ethyl 2-[(2-*N*-*tert*.-butyloxycarbonylamino)ethoxy]benzoate



The preparation was carried out in analogy to example 15A starting from ethyl salicylate.

Yield: 86% of theory

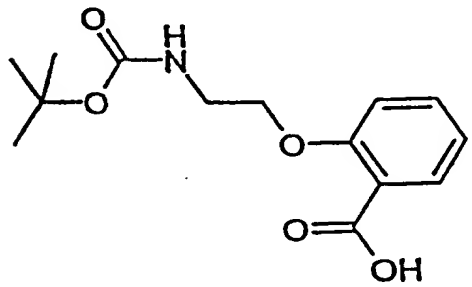
^{1}H-NMR (200 MHz, DMSO-*d6*): 1.41 (t, 3H, J=7Hz); 1.45 (s, 9H), 3.58 (dt, 2H, J=6 and 6Hz), 4.12 (t, 2H, J=6Hz), 4.38 (q, 2H, J=7Hz), 5.58 (br s, 1H), 6.91-7.08 (m, 2H), 7.48 (dt, 1H, J=8and 0.5Hz), 7.84 (dd, 1H, J=8 and 0.5Hz);

MS (DCI/NH_3) $C_{16}H_{23}NO_5$ m/e calc 309.4; found 295 ($M+NH_4^+$);

Rf 0.09 (toluene / ethyl acetate = 20/1).

Example 41A

2-[(2-*N*-*tert*.-butyloxycarbonylamino)ethoxy]benzoic acid



To a stirred solution of ethyl 2-(2-*N*-*tert*-butoxycarbonylaminoethoxy)benzoate (example 40A) (4.800 g, 15.51 mmol) in methanol (10 mL), water (10 mL) and THF (12 mL) at 0 °C was added lithium hydroxide monohydrate (0.781 g, 18.62 mmol). The mixture was allowed to warm to room temperature, stirred overnight, and evaporated *in vacuo* to remove methanol and water. The residue was diluted with water, cooled to 0 °C, and then 1N hydrochloric acid

(15 mL) was added dropwise. The aqueous mixture was extracted with two portions of ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*.

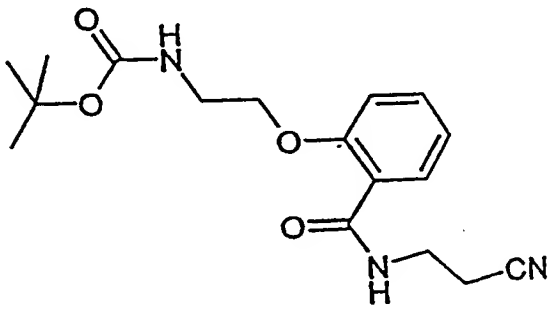
Yield 4.230 g, (97% of theory), white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 3.60-3.66 (m, 2H), 4.31 (t, 3H, J=5.2 Hz), 4.98 (br s, 1H), 7.05 (d, 1H, J=8.3 Hz), 7.11-7.17 (m, 1H), 7.52-7.58 (m, 1H), 8.18 (dd, 1H, J=1.8, 7.8 Hz);

MS (FAB) $C_{14}H_{19}NO_5$ m/e calc 281.3; found 282 (MH^+),

Example 42A

2-(2-*tert*-butoxycarbonylaminoethoxy)-*N*-(2-cyanoethyl)benzamide



To a stirred solution of 2-(2-*tert*-butoxycarbonylaminoethoxy)benzoic acid (1.700 g, 6.043 mmol) and 2-aminopropylnitrile (0.466 g, 6.647 mmol) in acetonitrile (40 mL) was added triethylamine (0.884 mL, 6.345 mmol) followed by 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2.134 g, 6.647 mmol). After stirred for 5 hours, the mixture was diluted with ethyl acetate, washed successively with 0.5N hydrochloric acid, water, saturated sodium bicarbonate, water and brine, dried over sodium sulfate, filtered, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane, ethyl acetate, 1:2).

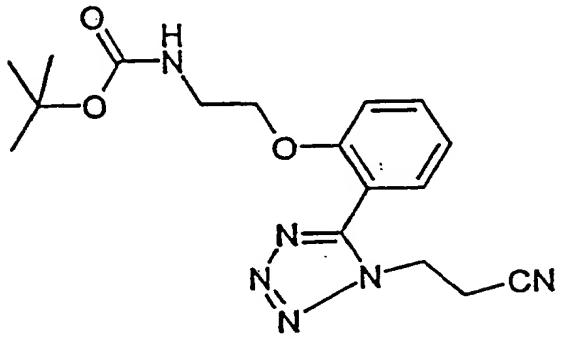
Yield 1.897 g, (94% of theory), white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.44(s, 9H), 2.78 (t, 2H, J=6.5 Hz), 3.62-3.68 (m, 2H), 3.75-3.82 (m, 2H), 4.18 (t, 2H, J=4.8 Hz), 5.09 (br, 1H), 6.95 (d, 1H, J=8.2 Hz), 7.06-7.12 (m, 1H), 7.41-7.48 (m, 1H), 8.20 (dd, 1H, J=1.8, 7.8 Hz), 8.52 (br s, 1H);

MS (FAB) $C_{17}H_{23}N_3O_4$ m/e calc 333.4; found 334 (MH^+).

Example 43A

N-(*tert*-butoxycarbonyl)-2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethylamine



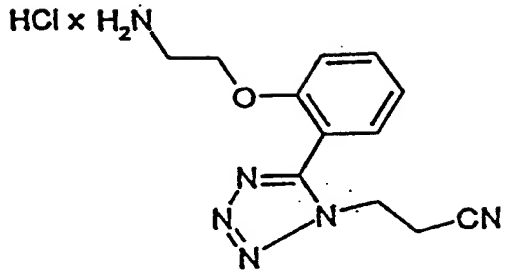
To a stirred solution of 2-(2-*tert*-butoxycarbonylaminoethoxy)-*N*-(2-cyanoethyl)benzamide (1.870 g, 5.609 mmol) in acetonitrile (10 mL) was added triphenylphosphine. The mixture was heated with a heat gun until a clear solution resulted and then cooled to 0 °C. Upon cooling to 0 °C, a precipitate formed. Diethyl azodicarboxylate (0.883 mL, 5.609 mmol) and azidotrimethylsilane (0.744 mL, 5.609 mmol) were added, alternating 10 drops at a time, starting with diethyl azodicarboxylate. The mixture was warmed to 40 °C, stirred for 1 hour, and stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and water, and the separated aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed successively with saturated sodium bicarbonate, water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (n-hexane / ethyl acetate = 1/2) to give an unseparable mixture of *N*-(*tert*-butoxycarbonyl)-2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethylamine (0.897 g, 45%) and the starting material (1.250 g, 67%) as colorless oil, which was used for the next step without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.54 (s, 9H), 3.06 (t, 2H, J=7.0 Hz), 3.39-3.46 (m, 2H), 4.10-4.20 (m, 2H), 4.55 (t, 2H, J=7.07 Hz), 4.74 (br s, 1H), 7.06-7.12 (m, 1H), 7.15-7.20 (m, 1H), 7.50-7.59 (m, 2H);

MS (FAB) $C_{17}H_{22}N_6O_3$ m/e calc 358.4; found 359 (MH^+).

Example 44A

2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethylamine hydrochloride

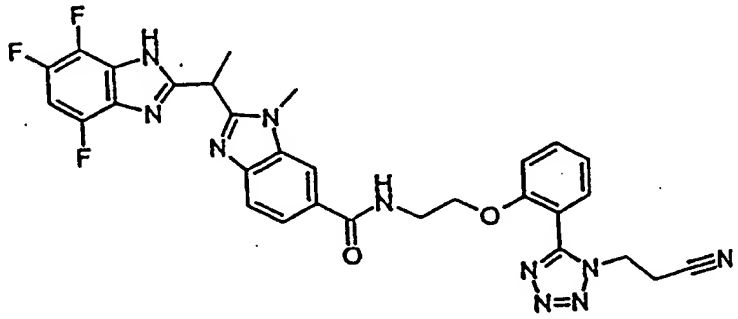


N-(*tert*-butoxycarbonyl)-2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethylamine (0.976 g) was dissolved in 1,4-dioxane (2.0 mL), and treated with 4N HCl in 1,4-dioxane (5.0 mL). After stirred for 2 hours, the mixture was concentrated *in vacuo* to give a mixture of 2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethylamine hydrochloride, 2-[2-(2-cyanoethylcarbamoyl)phenoxy]ethylamine hydrochloride and 2-[2-(2-ccarbamoylethylcarbamoyl)phenoxy]ethyl amine as colorless amorphous (0.700 g), which was used for the next step without further purification.

MS (FAB) $C_{12}H_{14}N_6O$ m/e calc 258.3; found 259 (MH^+).

Example 45A

N-[2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide

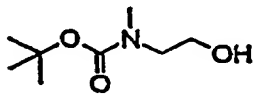


The product (0.378 g) obtained in example 44A was dissolved in *N,N*-dimethylformamide, and then 1-hydroxybenzotiazole (0.217 g, 1.603 mmol) and triethylamine (0.343 mL, 2.458 mmol) were added. The mixture was stirred for 5 minutes before 3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxilic acid (0.400 g, 1.069 mmol) was added. After the mixture was stirred for 5 minutes, water soluble cardodiimide hydrochloride (0.246 g, 1.282 mmol) was added. The mixture was stirred overnight,

partitioned between ethyl acetate and water, and the layer were separated, and then the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (chloroform / methanol = from 3/97 to 5/95) to give *N*-[2-[2-(2-carbamoylethylcarbamoyl)phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide (0.112 g) as a white solid and an unseparable mixture of *N*-[2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide and *N*-[2-[2-(2-cyanoethylcarbamoyl)phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide as white solid (0.485 g) which was used for the next step without further purification.
MS (FAB) m/e 615 (MH^+);

Example 46A

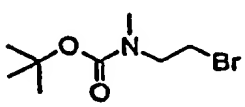
tert-Butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate



tert-Butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate was prepared by the procedure described in *Bull. Chem. Soc. Jpn* 50 718-721 (1977) from 2-(methylamino)ethanol (4.0g, 53.3 mmol).
Yield 7.33g (79% of theory), colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): 1.47 (s, 9H), 2.92 (s, 3H), 3.40 (t, 2H, J=5.3 Hz), 3.75 (q, 2H, J=5.3Hz);
MS (FAB) $C_8H_{17}NO_3$ m/e calc 175.2; found 176 (MH^+);
Rf 0.31 (ethyl acetate / n-hexane = 1/1).

Example 47A

tert-Butyl *N*-(2-bromoethyl)-*N*-methylcarbamate

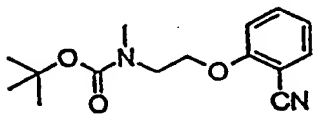


To a solution of *tert*-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (7.21 g, 41.1 mmol, 1.0 eq.) and *N,N*-diisopropylethylamine (8.0 mL, 45.9 mmol, 1.1 eq.) was added methanesulfonyl chloride (5.0 g, 43.6 mmol, 1.06 eq.) at cooling by ice bath and stirred at room temperature for

1 hour. The solvent was evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (120 mL), to this solution was added lithium bromide (34.0 g, 392mmol) and stirred for 2 days. The reaction mixture was poured into water and extracted into ethyl acetate. The organic layer was washed by brine, dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography on silica (ethyl acetate / n-hexane = 1/6).
Yield 2.14g (22% of theory), colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): 1.47 (s, 9H), 2.93 (s, 3H), 3.44 (t, 2H, J=6.8 Hz), 3.59 (t, 2H, J=6.8 Hz);
Rf 0.32 (ethyl acetate / n-hexane = 1/6).

Example 48A

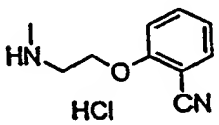
tert-Butyl *N*-[2-(2-cyanophenoxy)ethyl]-*N*-methylcarbamate



The preparation was carried out in analogy to example 15A starting from *tert*-butyl *N*-(2-bromoethyl)-*N*-methylcarbamate and 2-hydroxybenzonitrile (example 47A) (802.3 mg).
Yield 287.3 mg (31% of theory), colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): 1.47 (s, 9H), 3.08 (s, 3H), 3.67 (t, 2H, J=5.2 Hz), 4.11-4.22 (m, 2H), 6.95-7.02 (m, 2H), 7.44-7.55 (m, 2H);
MS (FAB) $C_{15}H_{20}N_2O_3$ m/e calc 276.3; found 277 (MH^+);
Rf 0.15 (ethyl acetate / n-hexane = 1/4).

Example 49A

2-[2-(Methylamino)ethoxy]benzonitrile hydrochloride

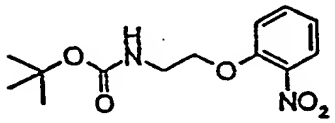


The preparation was carried out in analogy to example 18A strating from *tert*-butyl *N*-[2-(2-cyanophenoxy)ethyl]-*N*-methylcarbamate (example 48A) (285 mg).
Yield 95.9 mg (44% of theory), colorless powder
^{1}H-NMR (300 MHz, CD_3OD): 2.90(s, 3H), 3.57 (t, 2H, J=4.9 Hz), 4.48 (t, 2H, J=4.9 Hz), 7.20 (dt, 1H, J=0.6, 7.6 Hz), 7.27 (dd, 1H, J= 0.6, 8.5 Hz), 7.68-7.74 (m, 2H);

MS (FAB) $C_{10}H_{12}N_2O.HCl$ m/e calc 176.2; found 177 (MH^+).

Example 50A

tert-Butyl *N*-[2-(2-nitrophenoxy)ethyl]carbamate



To a solution of 2-nitrophenol (4.991 g, 35.9 mmol, 1.2 eq.) and potassium carbonate (4.959 g, 35.9 mmol, 1.2 eq.) in *N,N*-dimethylformamide (50 mL) was heated at 40 °C for 30 minutes. To this solution was added *tert*-butyl-*N*-(2-bromoethyl)carbamate (6.7 g 29.9 mmol, 1.0 eq.) and sodium iodide (0.01 g, 0.067 mmol, catalytic amount) and stirred at 60 °C for overnight. The reaction mixture was poured into water and extracted into ethyl ether. The organic layer was washed by water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica (n-hexane / ethyl acetate = from 2/1 to 1/1).

Yield 4.34 g (52% of theory), pale yellow solid.

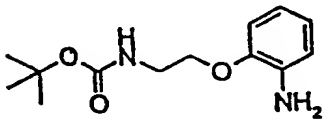
^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 3.58 (dt, 2H, J=5.6, 5.0 Hz), 4.17 (t, 2H, J=5.0 Hz), 5.14 (br s, 1H), 7.02-7.08 (m, 2H), 7.50-7.56 (m, 1H), 7.86 (dd, 1H, J=1.7, 8.1 Hz);

MS (FAB) $C_{13}H_{18}N_2O_5$ m/e calc 282.3; found 283 (MH^+);

Rf 0.34 (n-hexane / ethyl acetate = 2/1).

Example 51A

tert-Butyl *N*-[2-(2-aminophenoxy)ethyl]carbamate



A solution of *tert*-butyl *N*-[2-(2-nitrophenoxy)ethyl]carbamate (example 50A) (2.99 g, 10.6 mmol) in methanol (30 mL) was stirred under an atmosphere of hydrogen over 10% Pd-C for 5 hours. The reaction mixture was filtrated on Celite and washed with methanol several times. the filtrate was concentrated *in vacuo*.

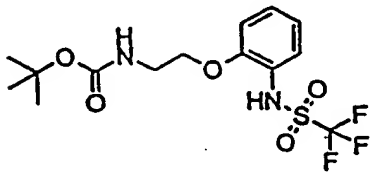
Yield 2.38g (89% of theory), pale gray solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 3.55 (dt, 2H, J=5.3, 5.1 Hz), 4.06 (t, 2H, J=5.1Hz), 4.95 (br s, 1H), 6.89 (dd, 1H, J=1.1, 8.2 Hz), 6.95-7.00 (m, 1H), 7.16-7.21 (m, 1H), 7.52 (dd, 1H, J=1.5, 8.0 Hz), 7.86 (br s, 1H);

MS (FAB) $C_{13}H_{20}N_2O_3$ m/e calc 252.3; found 253 (MH^+);
Rf 0.33 (n-hexane / ethyl acetate = 2/1).

Example 52A

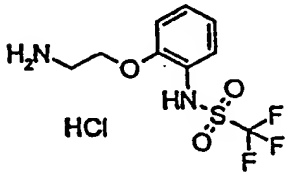
Tert-butyl *N*-[2-(2-trifluoromethanesulfonamidophenoxy)ethyl]carbamate



To a solution of *tert*-butyl *N*-[2-(2-aminophenoxy)ethyl]carbamate (example 51A) (0.80 g, 3.17 mmol, 1.0 eq.) and trifluoromethanesulfonic anhydride (0.587 mL, 3.49 mmol, 1.1 eq.) in dichloromethane (10 mL) was added triethylamine (0.53 mL, 3.81 mmol, 1.2 eq.) at 0 °C and stirred at room temperature for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed by 0.5N hydrochloric acid, water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica (n-hexane / ethyl acetate = 3/1).
Yield 0.769 g (63% of theory), colorless oil.
^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 3.54 (dt, 2H, J=6.3, 5.2 Hz), 4.11 (t, 2H, J=5.2 Hz), 4.91 (br s, 1H), 6.67-6.84 (m, 4H);
MS (FAB) $C_{14}H_{19}F_3N_2O_5S$ m/e calc 384.4; found 385 (MH^+).

Example 53A

N-[2-(2-Aminoethoxy)phenyl]trifluoromethanesulfonamide hydrochloride

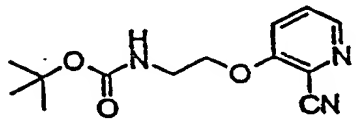


The preparation was carried out in analogy to example 18A starting from *tert*-butyl *N*-[2-(2-trifluoromethanesulfonamidophenoxy)ethyl]carbamate (example 52A) and afforded a white solid. Yield 95%.
^{1}H-NMR (300 MHz, DMSO-*d6*): 3.21-3.35 (m, 2H), 4.22 (t, 2H, J=5.0 Hz), 7.02 (dt, 1H, J=1.1, 7.7 Hz), 7.12 (dd, 1H, J=0.9, 8.2 Hz), 7.28-7.35 (m 2H), 8.21 (br s, 3H), 11.18 (br s, 1H);

MS (FAB) $C_9H_{11}F_3N_2O_3S.HCl$ m/e calc 284.3; found 285 (MH^+).

Example 54A

tert-Butyl *N*-[2-(2-cyanopyridin-3-yl)ethyl]carbamate



The preparation was carried out in analogy to example 15A starting from 2-cyano-3-hydroxypyridine (Synthesis 1983, 316) (1.185 g).

Yield 648.9 mg (47% of theory), colorless oil.

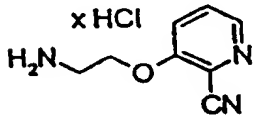
^{1}H-NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 3.61 (dt, 2H, J=5.9 5.2 Hz), 4.18 (t, 2H, J=5.2 Hz), 5.04 (br s, 1H), 7.36 (dd, 1H, J=1.2, 8.7 Hz), 7.47 (dd, 1H, J=4.5, 8.7 Hz), 8.31 (dd, 1H, J=1.2, 4.5Hz);

MS (FAB) $C_{13}H_{17}N_3O_3$ m/e calc 263.3; found 264 (MH^+);

Rf 0.19 (ethyl acetate / n-hexane = 1/1).

Example 55A

3-(2-Aminoethoxy)-2-cyanopyridine hydrochloride



The preparation was carried out in analogy to example 18A starting from *tert*-butyl *N*-[2-(2-cyanopyridin-3-yl)ethyl]carbamate (example 54A) (647 mg).

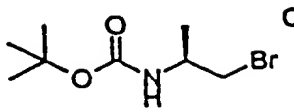
Yield 448.3 mg (77% of theory), colorless powder.

^{1}H-NMR (300 MHz, CD_3OD): 3.49 (t, 2H, J=5.0 Hz), 4.49 (t, 2H, J=5.0 Hz), 7.79 (dd, 1H, J=4.5, 8.8 Hz), 7.78 (dd, 1H, J=1.2, 8.8 Hz), 8.36 (dd, 1H, J=1.2, 4.5Hz);

MS (FAB) $C_8H_9N_3O_3.xHCl$ m/e calc 163.2; found 164 (MH^+).

Example 56A

(S)-2-[(*N*-tert.-Butyloxycarbonyl)amino]-1-bromopropane



To a mixture of Boc-L-alaninol (3.00 g, 17.2 mmol) and N,N-diisopropylethylamine (3.6 mL, 20.5 mmol) in dichloromethane (9 mL) was added dropwise methanesulfonyl chloride (1.59 mL, 20.5 mmol) under an ice cooling. The reaction mixture was stirred at room temperature for 3 hours. After evaporation of volatiles *in vacuo*, tetrahydrofuran (18 mL) and lithium bromide (2.97 g, 34.2 mmol) was added to the residue. The resulted suspension was stirred at room temperature for 24 hours, then the mixture was heated to 50 °C for 5 hours. The mixture was concentrated, dissolved in water, extracted with ethyl acetate, dried and evaporated. Purification by silica gel column chromatography (n-hexane/ethyl acetate = 10/1 to 5/1 eluent).

Yield 1.61g (39 % of theory), colorless solid.

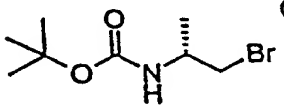
^{1}H-NMR (300MHz, $CDCl_3$): 1.24 (d, 3H, J=6.7 Hz), 1.45 (s, 9H), 3.43-3.66 (m, 2H), 3.93-4.00 (m, 1H), 4.66 (br s, 1H);

mp 44.9-45.8 °C;

Rf = 0.6 (n-hexane/ethyl acetate = 2/1).

Example 57A

(R)-2-[(*N-tert.*-Butyloxycarbonyl)amino]-1-bromopropane



The preparation was carried out in analogy to example 56A starting from Boc-D-alaninol.

Yield 42% of theory.

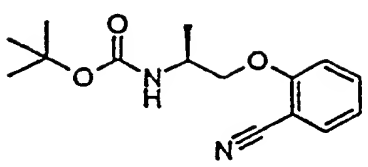
^{1}H-NMR (300 MHz, $CDCl_3$) : 1.24 (d, 3H, J=6.7 Hz), 1.45 (s, 9H), 3.43-3.63 (m, 2H), 3.93-3.98 (m, 1H), 4.66 (br s, 1H);

mp 44.8-45.8 °C;

Rf = 0.6 (n-hexane/ethyl acetate = 2/1).

Example 58A

(S)-2-[2-[(*N-tert.*-Butyloxycarbonyl)aminopropoxy]benzonitrile



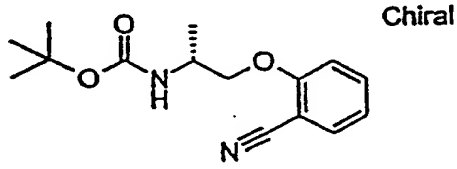
To a suspended mixture of 2-cyanophenol (250 mg, 2.10 mmol) and cesium carbonate (753 mg, 2.31 mmol) in N,N-dimethylformamide (6 mL) was added example 56A (500 mg, 2.1 mmol) at room temperature. The reaction mixture was stirred at ambient temperature for 3 days. After an additional stirring at 50 °C for 5 hours, the reaction mixture was quenched with water. The mixture was extracted with ethyl acetate, washed with brine, dried and concentrated. Purification by silica gel column chromatography (n-hexane/ethyl acetate = 10/1 to 4/1 eluent) yielded 306 mg of a colorless oil that consist of the target molecule and 2-cyanophenol (ca. 1 : 1).

MS (FAB) $C_{15}H_{20}N_2O_3$ m/e calc 276.3; found 277 (MH^+);

Rf 0.55 (n-hexane/ethyl acetate = 1/1).

Example 59A

(R)-2-[2-[(*N-tert.*-Butyloxycarbonyl)aminopropoxy]benzonitrile



The preparation was carried out in analogy of example 58A starting from example 57A.

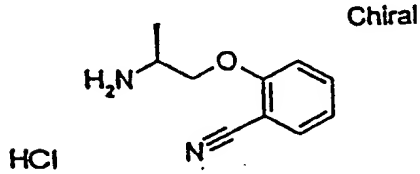
mixture of the product & 2-cyanophenol (1:1)

MS (FAB) $C_{15}H_{20}N_2O_3$ m/e calc 276.3; found 277 (MH^+);

Rf 0.55 (n-hexane/ethyl acetate = 1/1).

Example 60A

(S)-2-[2-aminopropoxy]benzonitrile hydrochloride



To a solution of example 58A (306 mg) in 1,4-dioxane (4 mL) was added 4N-hydrochloric acid in 1,4-dioxane (4 mL) at room temperature. The mixture was stirred at ambient

temperature for 1 hour. A large volume of diethyl ether was poured into the reaction mixture until a white precipitate was observed. The precipitate was collected by filtration, washed with diethyl ether and dried.

Yield 115 mg (26% yield in 2 steps from example 56A), white solid

^{1}H-NMR (300 MHz, DMSO-d_6): 1:34 (d, 3H, J=6.7 Hz), 3.61- 3.67 (m, 1H), 4.25-4.28 (m, 2H), 7.16 (dt, J=0.5, 7.6 Hz), 7.31 (d, J=8.5 Hz), 7.66-7.72 (m, 1H), 7.77 (dd, 1H, J=7.6, 1.7 Hz), 8.28 (br s, 3H);

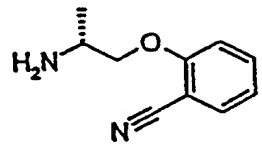
MS (FAB) $C_{10}H_{12}N_2O$.HCl m/e calc 176.2; found 177 (MH^+);

mp 178.3-180.4 °C.

Example 61A

(R)-2-[2-aminopropyl-1-oxy]benzonitrile hydrochloride

Chiral



HCl

The preparation was carried out in analogy to example 60A starting from example 59A.

Yield 21% yield in 2 steps from example57A, white solid

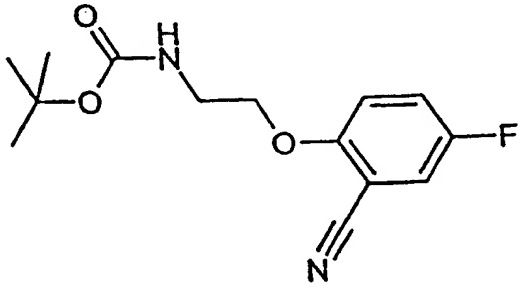
^{1}H-NMR (300 MHz, DMSO-d_6): 1.34 (d, 3H, J=6.7 Hz), 3.61-3.67 (m, 1H), 4.24-4.27 (m, 2H), 7.16 (dt, J=0.6, 7.6 Hz), 7.31 (d, J=8.5 Hz), 7.66-7.72 (m, 1H), 7.77 (dd, 1H, J=7.6, 1.7 Hz), 8.23 (br s, 3H);

MS (FAB) $C_{10}H_{12}N_2O$.HCl m/e calc 176.2; found 177 (MH^+);

mp 174.1-177.0 °C.

Example 62A

2-[(2-N-Tert.-butyloxycarbonylamino)ethyl-1oxy]-5-fluoro-benzonitrile



The preparation was carried out in analogy to example 15A starting from 2-cyano-4-fluorophenol (EP152014).

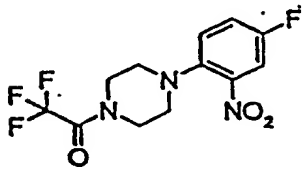
Yield: 50% of theory; white solid

^{1}H-NMR (300 MHz, DMSO-d_6): 1.45 (s, 9H), 3.58 (dt, 2H, J=6 and 6Hz), 4.08-4.16 (m, 2H), 5.06 (s, 1H), 6.93 (dd, 1H, J=4.0, 9.0Hz) 7.21-7.30 (m, 2H);

MS (FAB) $C_{14}H_{17}FN_2O_3$ m/e calc 280.3; found 281 (MH^+);

Example 63A

1-(4-Fluoro-2-nitrophenyl)-4-trifluoroacetylpiperazine



To trifluoroacetic anhydride (25 mL) was added 1-(4-fluorophenyl)piperazine (3.0 g, 16.65 mmol, 1.0 eq.) and potassium nitrate (1.851 g, 18.31 mmol, 1.1 eq.) was added at 0 °C and stirred at 0 °C for 1 hour and at room temperature for overnight. The reaction mixture was poured into ice, neutrized by sat. $NaHCO_3$ aq. and extracted into ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ aq., water and brine, dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography on silica (ethyl acetate / n-hexane = 4/1).

Yield 4.642 g (87% of theory), brown solid.

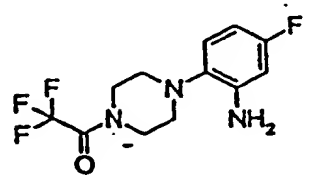
^{1}H-NMR (300 MHz, $CDCl_3$): 3.06-3.10 (m, 4H), 3.76 (t, 2H, J=4.7 Hz), 3.85 (t, 2H, J=5.0 Hz), 7.22 (dd, 1H, J=4.9, 9.0 Hz), 7.30 (dd, 1H, J=3.0, 9.0 Hz), 7.55 (dd, 1H, J=3.0, 7.8Hz);

MS (FAB) $C_{12}H_{11}F_4N_3O_3$ m/e calc 321.2; found 322 (MH^+);

Rf 0.40 (ethyl acetate / n-hexane = 1/4).

Example 64A

1-(2-Amino-4-fluorophenyl)-4-trifluoroacetylpiperazine



The preparation was carried ut in analogy to example 51A starting from example 63A.

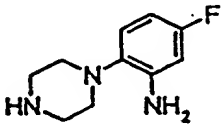
Yield 84% of theory, colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): 2.91-2.93 (m, 4H), 3.73 (m, 4H), 4.09-4.16 (m, 2H), 6.38-6.47 (m, 2H), 6.90 (dd, 1H, J=5.7, 8.5 Hz);

MS (FAB) $C_{12}H_{13}F_4N_3O$ m/e calc 291.3; found 292 (MH^+).

Example 65A

1-(2-Amino-4-fluorophenyl)piperazine



To a solution of 1-(2-Amino-4-fluorophenyl)-4-trifluoroacetylpiperazine (1.00 g 3.433 mmol, 1.0 eq.) in ethanol (10 mL) was added sodium borohydride (0.13 g ,3.433 mmol, 1.0 eq.) at 0 °C and stirred at 0 °C for 1 hour and at room temperature for overnight. The reaction mixture was concentrated, diluted with water, and extracted into chloroform. The organic layer was dried over K_2CO_3, filtrated and evaporated.

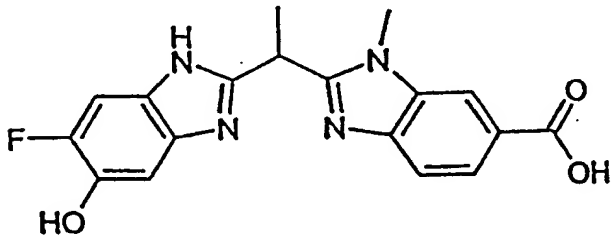
Yield 543 mg (81% of theory), white solid

^{1}H-NMR (300 MHz, $CDCl_3$): 2.80-2.83 (m, 4H), 2.99-3.02 (m, 4H), 4.13 (br, 2H), 6.36-6.45 (m, 2H), 6.92 (dd, 1H, J=5.8, 8.4 Hz);

MS (FAB) $C_{10}H_{14}FN_3$ m/e calc 195.2; found 196 (MH^+).

Example 66A

2-[1-(6-fluoro-5-hydroxy-1H-benzoimidazol-2-yl)ethyl]-3-methyl-3H-benzoimidazole-5-carboxylic acid



To a solution of 2-[1-(5-benzyloxy-6-fluoro-1H-benzoimidazol-2-yl)ethyl]-3-methyl-3*H*-benzoimidazole-5-carboxylic acid (example 13A) (0.50g, 1.13mmol) in methanol (30 mL) was added 10% palladium on carbon (10% Pd-C) (0.40g) and stirred under an atmosphere of hydrogen at 2 - 3 atoms for 4 hours. The reaction mixture was filtered through celite. The filtrate was condensed under reduced pressure and dried *in vacuo*.

Yield: 0.25g (62.7% of theory), colorless powder

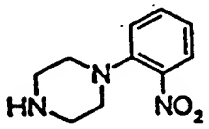
^{1}H-NMR (300 MHz, DMSO-d_6): 1.82 (d, 3H, J=7.1 Hz), 3.77 (s, 3H), 4.86 (q, 1H, J=7.1 Hz), 6.99 - 7.01 (m, 1H), 7.18 - 7.25 (m, 1H), 7.57 (d, 1H, J=8.4 Hz), 7.81 (dd, 1H, J=8.4, 1.4 Hz), 8.07 (s, 1H);

MS (FAB) $C_{11}H_{15}FN_4O_3$ m/e calc 354.3; found 355 (MH^+);

Rf 0.10 (acetic acid / methanol / ethyl acetate = 1 / 20 / 80).

Example 67A

1-(2-Nitrophenyl)piperazin



To a stirred solution of piperazine (15.26 g, 177.18 mmol) in tetrahydrofuran (100 mL) was added 2-fluoronitrobenzene (5.00 g, 35.44 mmol) and stirred at room temperature for 4 hours. The reaction mixture was concentrated in vacuo and diluted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The crude orange oil (10.13 g) was used for the next step without further purification.

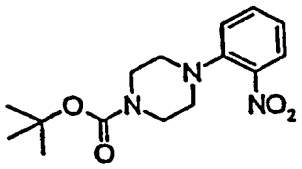
^{1}H-NMR (300 MHz CDCl3): 2.95-3.66 (m, 8H), 7.02 (dt, 1H, J= 8.3, 2.0 Hz), 7.13 (dd, 1H, J=8.3, 1.1 Hz), 7.44-7.50 (m, 1H), 7.74 (dd, 1H, J=8.1, 1.6 Hz);

MS (FAB) $C_{10}H_{13}N_3O_2$ m/e calc 207.2; found 208 (MH^+);

Rf 0.25 (chloroform / methanol = 10/1).

Example 68A

1-*tert*-Butoxycarbonyl-4-(2-nitrophenyl)piperazine



To a stirred solution of 1-(2-nitrophenyl)piperazin (example 67A) (10.13 g, 48.88 mmol) in dichloromethane (100 mL) was added triethylamine (3.41 mL, 24.44 mmol) and di-*tert*-butyl dicarbonate (21.34 g, 97.76 mmol). The mixture was stirred at room temperature for 12 hours. The reaction was concentrated *in vacuo*. Purification by silica gel column chromatography twice (from n-hexane only to n-hexane / ethyl acetate = from 25/1 to 4/1, twice) afforded

yellow oil (16.12 g) contaminated with di-*tert*-butyl dicarbonate (ca. 30%) which was used for the next step without further purification.

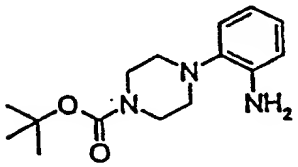
^{1}H-NMR (300 MHz, $CDCl_3$): 1.48 (s, 9H), 1.53 (s, 8H), 3.01 (t, 4H, J=4.9 Hz), 3.58 (t, 4H, J=4.9 Hz), 7.06-7.16 (m, 2H), 7.46-7.50 (m, 1H) 7.77 (dd, 1H, J=8.1, 1.6 Hz);

MS (FAB) $C_{15}H_{21}N_3O_4$ m/e calc 307.4; found 308 (MH^+);

Rf 0.33 (n-hexane / ethyl acetate = 4/1).

Example 69A

1-*tert*-Butoxycarbonyl-4-(2-aminophenyl)piperazine



Under H_2 atmosphere (3 atm), the mixture of 1-*tert*-butoxycarbonyl-4-(2-nitrophenyl)piperazine (example 68A) (16.11 g, 34.59 mmol, containing di-*tert*-butyl carbonate), propylamine (1.42 mL, 17.30 mmol, to separate di-*tert*-butyl carbonate from target compound) and 10% Pd-C (1 g) in methanol (150 mL) was stirred at room temperature for 4 hours. The reaction mixture was filtered with celite pad and the filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (n-hexane / ethyl acetate = 9/1). Yield 8.61 g (88% of theory from 1-(2-fluorophenyl)piperidine), colorless solid.

^{1}H-NMR (300MHz, $CDCl_3$): 1.49 (s, 9H), 2.85 (t, 4H, J= 4.9 Hz), 3.55 (m, 4H), 3.97 (br s, 2H), 6.71-6.77 (m, 2H), 6.91-6.97 (m, 2H);

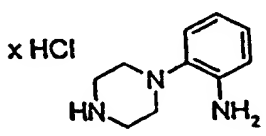
MS (FAB) $C_{15}H_{23}N_3O_2$ m/e calc 277.4; found 278 (MH^+);

mp. 120-122°C;

Rf 0.41 (n-hexane / ethyl acetate = 2/1).

Example 70A

1-(2-aminophenyl)piperazine, hydrochloride



The preparation was carried out in analogy to example 18A starting from example 69A.

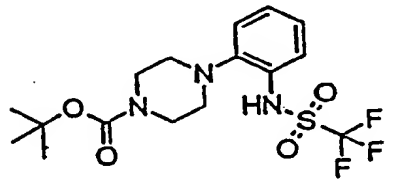
Yield 79% of theory, colorless solid

^{1}H NMR (300 MHz, DMSO-d_6): 3.09-3.19 (m, 4H), 3.28 (s, 4H), 3.85 (br s, 1H), 7.22-7.44 (m, 4H), 9.38 (br s, 2H);

MS (FAB) $C_{10}H_{13}N_3$·HCl m/e calc 276; found 278 (MH^+);

Example 71A

1-*tert*-Butoxycarbonyl-4-(2-trifluoromethanesulfonamidephenyl)piperazine



The preparation was carried out in analogy to example 52A starting from example 69A.

Yield 45% of theory, white solid

^{1}H-NMR (300 MHz, $CDCl_3$): 1.49 (s, 9H), 2.81 (t, 4H, J=4.9 Hz), 3.60 (br s, 4H), 7.14-7.26 (m, 3H), 7.56-7.60 (m, 1H);

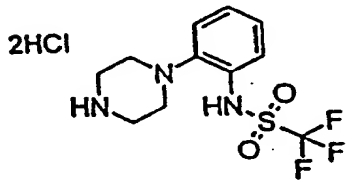
MS (FAB) $C_{16}H_{22}F_3N_3O_4S$ m/e calc 409.4; found 410 (MH^+);

mp. 115-118°C;

Rf 0.34 (n-hexane / ethyl acetate = 4/1).

Example 72A

1-(2-Trifluoromethanesulfonamidephenyl)piperazine



The preparation was carried out in analogy to example 18A starting from example 71A.

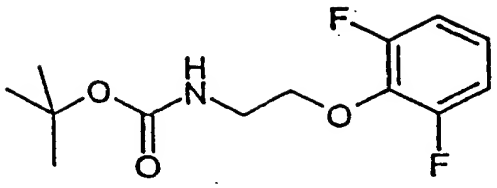
Yield 73% of theory, white solid

^{1}H-NMR (300 MHz DMSO-d_6): 3.06-3.09 (m, 4H), 3.16-3.21 (m, 4H), 7.20-7.40 (m, 4H);9.24 (br s, 2H);

MS (FAB) $C_{11}H_{14}F_3N_3O_2S$·HCl m/e calc 309; found 310 (MH^+);

Example 73A

2-(*N*-*tert*-Butyloxycarbonylamino)ethoxy-1,3-difluorobenzene



The preparation was carried out in analogy to example 15A starting from 2,6-difluorophenol.

Yield 55% of theory, colorless oil.

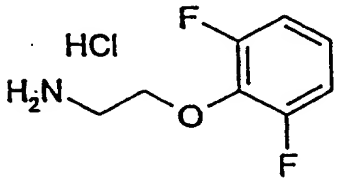
^{1}H-NMR (300 MHz $CDCl_3$): 1.45 (s, 9H), 3.44-3.51 (m, 2H), 4.17 (t, 2H, J=5.0 Hz), 5.10 (br s, 1H), 6.81-7.02 (m, 3H);

MS (FAB) $C_{13}H_{17}F_2NO_3$ m/e calc 273.2; found 274 (MH^+);

Rf 0.57 (n-hexane / ethyl acetate = 4/1).

Example 74A

2-Aminoethoxy-1,3-difluorobenzene hydrochloride



The preparation was carried out in analogy to example 18A starting from example 73A.

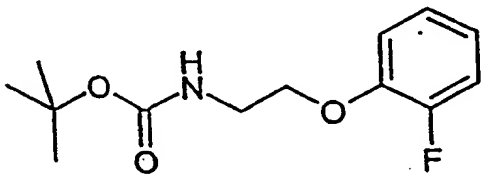
Yield 42% of theory, colorless solid.

^{1}H NMR (300 MHz DMSO-d_6): 3.49 (s, 2H), 4.43 (s, 2H), 6.80-6.99 (m, 3H), 8.47 (br s, 2H);

MS (FAB) $C_8H_9F_2NO$ HCl m/e calc 173; found 174 (MH^+).

Example 75A

1-[2-(*N-tert*-Butyloxycarbonylamino)ethoxy]-2-fluorobenzene



The preparation was carried out in analogy to example 15A starting from 2-fluorophenol.

Yield 71% of theory, colorless oil.

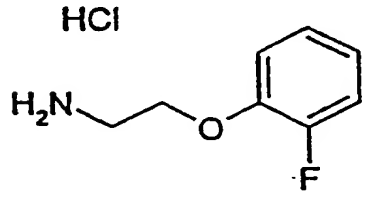
^{1}H NMR (300 MHz $CDCl_3$): 1.45 (s. 9H), 3.54 (q, 2H, J = 5.4 Hz), 4.09 (t, 2H, J = 5.1 Hz), 5.20 (br s, 1H), 6.88-7.11 (m, 1H);

MS (FAB) $C_{13}H_{17}F_2NO_3$ m/e calc 255.3; found 256 (MH^+);

Rf 0.34 (hexane/ethyl acetate = 4/1).

Example 76A

1-(2-aminoethoxy)-2-fluorobenzene



The preparation was carried out in analogy to example 18A starting from example 75A.

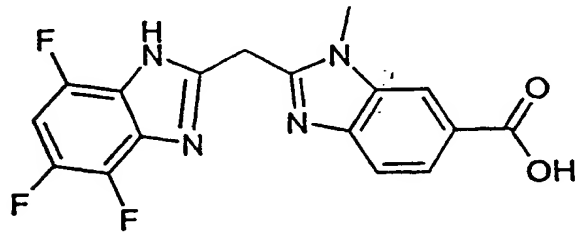
Yield 38% of theory, colorless solid.

^{1}H NMR (300 MHz DMSO-d_6): 3.23 (t, 2H, J = 5.2 Hz), 4.26 (t, 2H, J = 5.2 Hz), 6.97-7.03 (m, 1H), 7.13-7.28 (m, 3H), 8.18 (s, 2H);

MS (FAB) $C_2H_{10}FNO$ HCl m/e calc 155; found 156 (MH^+).

Example 77A

3-Methyl-2-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl-methyl)-3*H*-benzimidazole-5-carboxylic acid



A mixture of example 10A (0.75g; 2.91mmol), example 4A (0.51g; 3.05mmol) and DMPU (1,3-dimethyltetrahydro-2(*1H*)-pyrimidone; 2.5ml) was stirred under vacuum at 50°C for 2h to remove residual gases and heated to 200°C (bath temperature) for 1h under argon in a distillation apparatus to remove the reaction water. The DMPU was evaporated in vacuo and the warm residue was taken up in dichloromethane and stirred at room temperature for 2h. The product was collected by filtration and dried in vacuo.

Yield: 1.00g (96% of theory); grey crystalline solid

^{1}H-NMR (200 MHz, DMSO-d_6): 3.91 (s, 3H), 4.68 (s, 2H), 7.35 (cm, 1H), 7.62 (d, 1H, J= 9Hz), 7.81 (dd, 1H, J=9 and 0.5Hz), 8.20 (d, 1H, J=0.5Hz), 12.8 and 13.6 (2 br s, 2H);

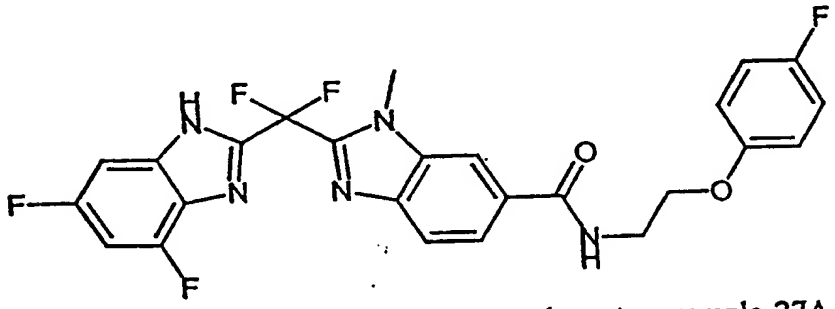
MS (DCI/NH_3) $C_{17}H_{11}F_3N_4O_2$ m/e calc 360.3; found 361 ($M+H^+$).

mp >250°C.

Preparation Examples

Example 1

2-[(4,6-Difluoro-1*H*-benzimidazol-2-yl)difluoromethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide.



The preparation was carried out in analogy to example 27A starting from difluoro malonic acid, example 21A, and 2-amino-4,6-difluoro-aniline.

Yield: 20% of theory; slightly yellow crystalline solid

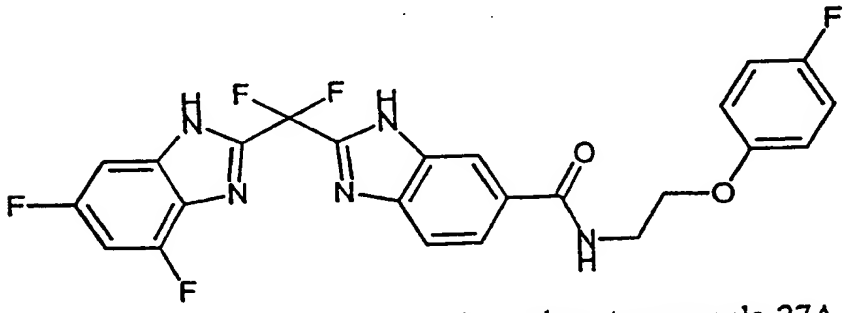
^{1}H-NMR (200 MHz, DMSO-d_6): 3.68 (dt, 2H, J=6 and 6Hz), 4.03 (s, 3H), 4.12 (t, 2H, J=6Hz), 6.95-7.40 (m, 6H), 7.80 (d, 1H, J=8Hz), 7.88 (dd, 1H, J=8 and 0.5Hz), 8.32 (d, 1H, J=0.5Hz), 8.81 (t, 1H, J=6Hz), 14.3 (br s, 1H);

MS (DCI/NH_3) $C_{25}H_{18}F_5N_5O_2$ m/e calc 515.4; found 516 ($M+H^+$);

R_f 0.66 (ethyl acetate)

Example 2

2-[(4,6-Difluoro-1*H*-benzimidazol-2-yl)difluoromethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3*H*-



The preparation was carried out in analogy to example 27A starting from difluoro malonic acid, example 22A, and 2-amino-4,6-difluoro-aniline.

Yield: 25% of theory; tan crystalline solid

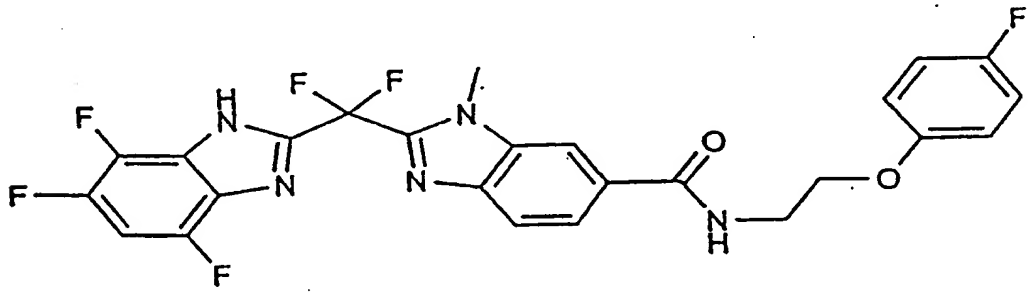
^{1}H-NMR (200 MHz, DMSO-*d6*): 3.65 (dt, 2H, J=6Hz and 6Hz), 4.10 (t, 2H, J=6Hz), 6.90-7.40 (m, 6H), 7.70 (d, 1H, J=8Hz), 7.90 (d, 1H, J=8Hz), 8.20 (s, 1H), 8.80 (t, 1H, J=6Hz), 14.10 (br, s, 1H)

MS (DCI/NH_3) $C_{24}H_{16}F_5N_5O_2$ m/e calc 501.4; found 502 ($M+H^+$);

R_f 0.61 (ethyl acetate)

Example 3

N-[2-(4-Fluorophenoxy)ethyl]-2-[(4,6,7-trifluoro-1*H*-benzimidazol-2-yl)difluoromethyl]-3*H*-benzimidazol-5-carboxamide

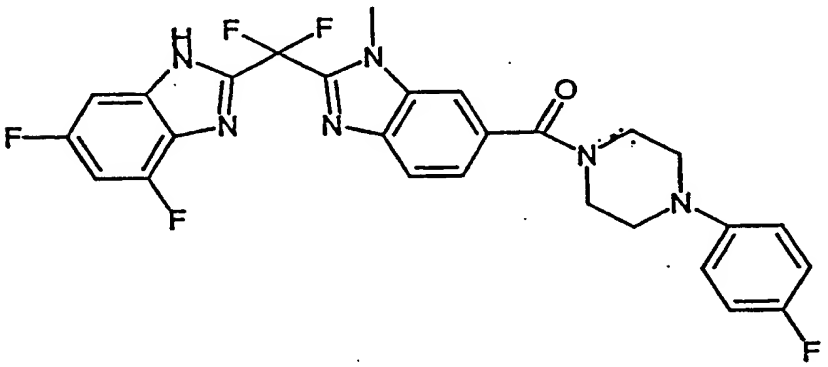


The preparation was carried out in analogy to example 27A starting from difluoro malonic acid, example 21A, and 2-amino-3,4,6-trifluoro-aniline.

Yield: 6% of theory; white crystalline solid

^{1}H-NMR (200 MHz, DMSO-*d6*): 3.66 (dt, 2H, J=6Hz and 6Hz), 3.99 (s,3H), 4.12 (t, 2H, J=6Hz), 6.90-7.90 (m, 7H), 8.28 (s, 1H), 8.80 (t, 1H, J=6Hz), 14.10 (br, s, 1H);
MS (DCI/NH_3) $C_{25}H_{17}F_6N_5O_2$ m/e calc 533.4; found 534 ($M+H^+$);
R_f 0.57 (ethyl acetate)

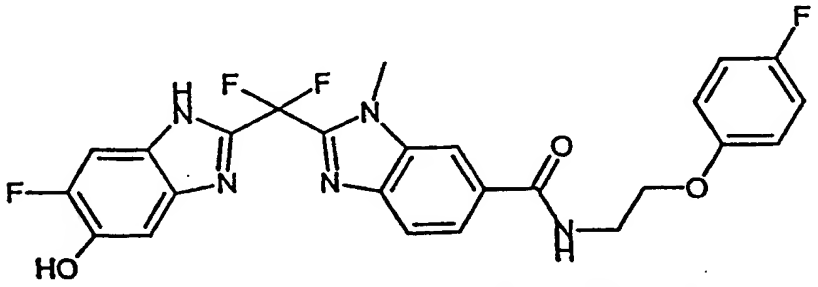
Example 4



The preparation was carried out in analogy to example 27A starting from difluoro malonic acid, example 24A, and 2-amino-4,6-difluoro-aniline.
Yield: 28% of theory; yellow crystalline solid
^{1}H-NMR (200 MHz, DMSO-*d6*): 3.12 (cm, 4H), 3.70 (cm, 4H), 4.00 (s, 3H), 6.90-7.50 (m, 7H), 7.86 (d, 1H, J=8Hz), 7.92 (s, 1H), 14.30 (br s, 1H);
MS (DCI/NH_3) $C_{27}H_{21}F_5N_6O$ m/e calc 540.5; found 541 ($M+H^+$);
R_f 0.55 (ethyl acetate)

Example 5

2-[(6-Fluoro-5-hydroxy-1*H*-benzimidazol-2-yl)difluoromethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide.



A solution of example 27A (1.13g; 1.86mmol) in methanol (100ml) was hydrogenated at 3 bar for 2h in the presence of palladium, 10 % on

charcoal (0.2g). The reaction mixture was filterd through kieselgur, washed with methanol and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silicagel (ethyl acetate:toluene=1:1).

Yield: 0.828g (87% of theory); white solid

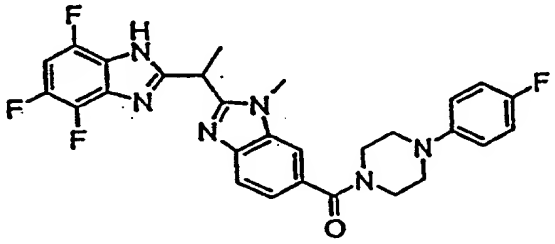
^{1}H-NMR (200 MHz, DMSO-d_6): 3.69 (dt, 2H, J=6Hz and 6Hz), 3.95 (s, 3H), 4.15 (t, 2H, J=6Hz), 6.90-7.25 (m, 5H), 7.48 (cm, 1H), 7.80 (d, 1H, J=8Hz), 7.88 (dd, 1H, J=8 and 0.5Hz), 8.31 (d, 1H, J=0.5Hz), 8.84 (t, 1H, J=6Hz), 10.00 (br s, 1H), 13.45 (br s, 1H);

MS (DCI/NH_3) $C_{25}H_{19}F_5N_3O_3$ m/e calc 513.5; found 514 ($M+H^+$);

R_f 0.42 (ethyl acetate)

Example 6

5-[4-(4-Fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



Method A:

To a stirred mixture of example 11A (21.8g; 58.2mmol), 1-(4-fluorophenyl)piperazine (10.5g; 58.2mmol) and N-methylmorpholine (7.36g; 72.8 mmol) in N,N-dimethylformamide (400ml) was added under argon at 0°C 1-hydroxybenzotriazole (10.2g; 75.7mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (12.3g; 64.1mmol). The mixture was allowed to warm to room temperature and stirring was continued for 3h. The solvent was evaporated in vacuo and the residue was partitioned between water (500ml) and ethylacetate (400ml). The aqueous layer was extracted with ethyl acetate (3 x 150ml). The combined organic layers were washed with sat. aq. NaCl solution, dried over $MgSO_4$, and evaporated in vacuo. The residue was treated with dichloromethane / cyclohexane and precipitated crude product was collected by filtration and dried in vacuo. For further purification the crude product was dissolved in a mixture of hot dichloromethane (300ml)/ethanol (150ml) and the dichloromethane was evaporated in vacuo. The ethanol solution was slowly cooled under stirring, the precipitated product was collected by filtration, washed with ethanol and dried in vacuo. This purification procedure was repeated twice.

Yield: 21.8g (70% of theory), white crystals

^{1}H-NMR (400 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 3.11 (cm, 5H), 3.65 (m, 3H), 3.80 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.95-7.10 (m, 4H), 7.27 (dd, 1H, J=8 and 0.5 Hz), 7.32 (cm, 1H), 7.65 (d, 1H, J= 8Hz), 7.68 (d, 1H, J=0.5Hz), 13.46 (br s, 1H);

MS (FAB) $C_{28}H_{24}F_4N_6O$ m/e calc 536.5; found 537 (MH^+);

m.p. 225-227°C ;

Rf 0.29 (ethyl acetate / methanol = 10/1).

Method B:

To a cooled (0 °C), stirred suspension of example 11A (1.00 g, 2.671 mmol, 1 eq) in *N,N*-dimethylformamide (10 mL) was added 1-(4-fluorophenyl)piperazine (0.48 g, 2.671 mmol, 1 eq), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.56 g, 2.939 mmol, 1.1 eq), 1-hydroxybenzotriazole (0.40 g, 2.939 mmol, 1.1 eq) and triethylamine (0.413 mL, 2.939 mmol, 1.1 eq). The mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated in vacuo and diluted with ethyl acetate. The organic layer was washed with water and sat. $NaHCO_3$ aq., dried over $MgSO_4$, filtered and concentrated. Purification was carried out by silica gel column chromatography (ethyl acetate / methanol = from 100/5 to 10/1 as eluent) and recrystallization twice (from ethyl acetate/diethyl ether = 1/5, chloroform/hexane = 1/5) to give white solid

Yield: 1.047 g (73% of theory)

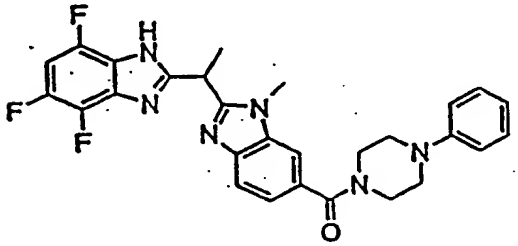
Method C:

To a stirred suspension of example 11A (0.70g; 1.87mmol) in dichloromethane (20ml) was added under Argon at -10°C triethylamine (0.38g; 3.74mmol), 1-(4-fluorophenyl)piperazine (0.34g; 1.87mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.39g; 2.06mmol). The mixture was allowed to warm to room temperature and stirring was continued for 15h. The mixture was diluted with dichloromethane and washed with water (50ml), sat. aq. $NaHCO_3$ solution (2 x 50ml), water (50ml), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified as described above in method A.

Yield: 0.67g (67% of theory), white crystals

Example 7

3-Methyl-5-(4-phenylpiperazin-1-ylcarbonyl)-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-phenylpiperazine (method B).

Yield: 37% of theory, colorless solid

^{1}H-NMR (300 MHz, DMSO-d_6): 1.87 (d, 3H, J=7.1 Hz), 3.17-3.20 (m, 4H), 3.41-3.65 (m, 4H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.80 (t, 1H, J=7.3 Hz), 6.95 (d, 2H, J=8.0 Hz), 7.20-7.27 (m, 2H), 7.25-7.34 (m, 1H), 7.63-7.68 (m, 2H), 13.46 (br s, 1H);

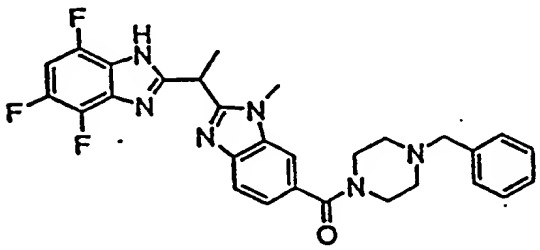
MS (FAB) $C_{28}H_{25}F_3N_6O$ m/e calc 518.5; found 519 (MH^+);

mp 246 °C;

R_f 0.43 (chloroform / methanol = 10/1).

Example 8

5-(4-Benzylpiperazin-1-ylcarbonyl)-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-benzylpiperazine (method B).

Yield: 60%. of theory; colorless powder

^{1}H-NMR (300 MHz, DMSO-d_6): 1.86 (d, 3H, J=7.1 Hz), 2.51 (m, 4H), 3.51 (m, 6H), 3.79 (s, 3H), 4.96 (q, 1H, J=7.1 Hz), 7.20 (dd, 1H, J=1.4, 8.3 Hz), 7.23-7.35 (m, 6H), 7.60-7.63 (m, 2H), 13.45 (br s, 1H);

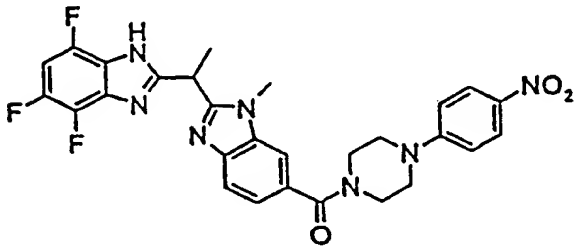
MS (FAB) $C_{29}H_{27}F_3N_6O$ m/e calc 532.57; found 533 (MH^+);

mp 260.7 °C (dec.);

Rf 0.36 (ethyl acetate / methanol = 10/1).

Example 9

3-Methyl-5-[4-(4-nitrophenyl)piperazin-1-ylcarbonyl]-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(4-nitrophenyl)piperazine (method B).

Yield: 32% of theory, yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 3.50-3.77 (m, 8H), 3.81 (s, 3H), 4.98 (q, 1H, J=7.1 Hz), 7.03 (d, 2H, J=9.5 Hz), 7.25-7.35 (m, 1H), 7.29 (d, 1H, J=8.3 Hz), 7.66 (d, 1H, J=8.3 Hz), 7.69 (d, 1H, J=0.8 Hz), 8.09 (d, 2H, J=9.5 Hz), 13.47 (br s, 1H);

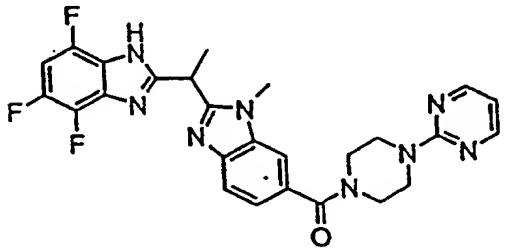
MS (FAB) $C_{28}H_{24}F_3N_7O_3$ m/e calc 563.5; found 564 (MH^+);

mp >260 °C;

Rf = 0.62 (chloroform / methanol = 9/1).

Example 10

3-Methyl-5-[4-(2-pyrimidyl)piperazin-1-ylcarbonyl]-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(2-pyrimidyl)piperazine (method B).

Yield: 25% of theory, colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6) 1.87 (d, 3H, J=7.1 Hz), 3.10-3.30 (m, 4H), 3.61-3.77 (m, 4H), 3.80 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.66 (t, 1H, J=4.7 Hz), 7.26 (d, 1H, J=9.5 Hz), 7.27-7.29 (m, 1H), 7.63-7.67 (m, 2H), 8.37 (d, 2H, J=4.7 Hz), 13.47 (br s, 1H);

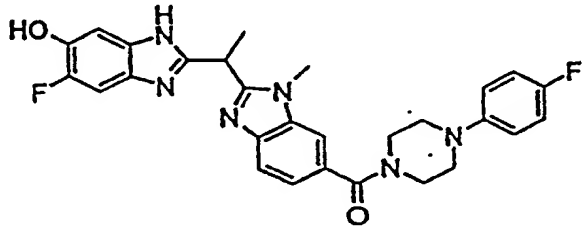
MS (FAB) $C_{26}H_{23}F_3N_8O$ m/e calc 520.5; found 521 (MH^+);

mp >260 °C;

Rf 0.30 (chloroform / methanol =10/1).

Example 11

2-[1-(5-Fluoro-6-hydroxy-1*H*-benzimidazol-2-yl)ethyl]-5-[4-(4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting example 66A and 1-(4-fluorophenyl)piperazine (method B).

Yield: 29% of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.83 (d, 3H, J=7.1 Hz), 3.11 (m, 4H), 3.30 (s, 3H), 3.65 (m 4H), 4.86 (q, 1H, J=7.1 Hz), 6.95-7.09 (m, 5H), 7.26 (dd, 2H, J=1.3, 8.3 Hz), 9.44 (br s, 1H), 12.07 (br s, 1H);

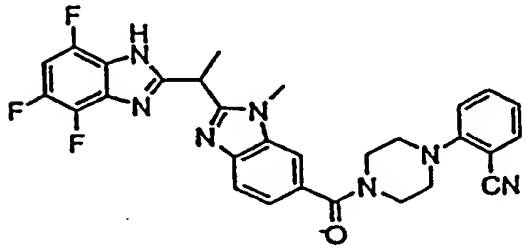
MS (FAB) $C_{27}H_{26}F_2N_6O_2$ m/e calc 516.6; found 517 (MH^+);

mp 189.5 °C (dec.);

Rf 0.20 (AcOEt / MeOH = 10/1).

Example 12

5-[4-(2-cyanophenyl)piperazin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1H-benzimidazol-2-yl)ethyl]-3H-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(2-cyanophenyl)piperazine (method B).

Yield: 53% of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.87 (d, 3H, J=7.1 Hz), 3.18 (m, 4H), 3.64 (m, 4H), 3.72 (s 3H), 4.98 (q, 1H, J=7.1 Hz) 7.13 (dd, 1H, J=7.5, 7.6 Hz), 7.20 (d, 1H, J=8.3 Hz), 7.28 (dd, 2H, J=1.3, 8.3 Hz), 7.59-7.74 (m, 4H), 13.47 (br s, 1H);

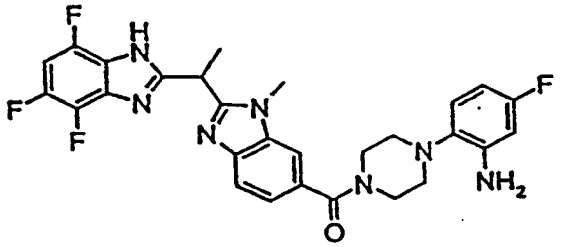
MS (FAB) $C_{29}H_{24}F_3N_7O$ m/e calc 543.6; found 544 (MH^+);

mp 254.3 °C (dec.);

Rf 0.56 (ethyl acetate / methanol = 10/1).

Example 13

5-[4-(2-Amino-4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and example 65A. (method B).

Yield: 51% of theory, pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): 1.87 (d, 3H, J=7.1 Hz), 2.67-2.89 (m, 4H), 3.43-3.90 (m, 4H), 3.81 (s, 3H), 4.98 (q, 1H, J=7.1 Hz), 5.18 (s, 2H), 6.23-6.30 (m, 1H), 6.44 (dd, 1H, J=2.9, 11.2 Hz), 6.90 (dd, 1H, J=6.1, 8.6 Hz), 7.25 (dd, 1H, J=1.4, 8.2 Hz), 7.29-7.35 (m, 1H), 7.65 (d, 1H, J=8.5 Hz), 7.66 (d, 1H, J=0.9 Hz), 13.46 (s, 1H);

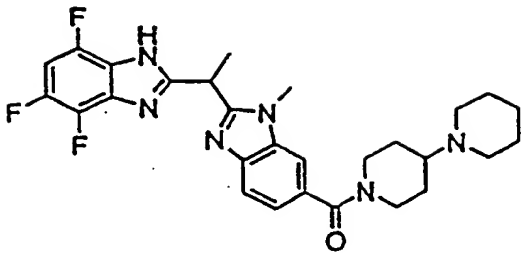
MS (FAB) $C_{28}H_{25}F_4N_7O$ m/e calc 551.5; found 552 (MH^+);

mp 234-239 °C;

Rf = 0.68 (chloroform / methanol = 9/1).

Example 14

5-(1,4'-Bipiperidiny-1'-ylcarbonyl)-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 4-piperidino-piperidine (method B).

Yield: 49% of theory, colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.23-1.85 (m, 10H), 1.87 (d, 3H, J=7.1 Hz), 2.50-3.30 (m, 9H), 3.80 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 7.20 (dd, 1H, J=8.3, 1.0 Hz), 7.25-7.34 (m, 1H), 7.60-7.63 (m, 2H), 13.40 (br s, 1H);

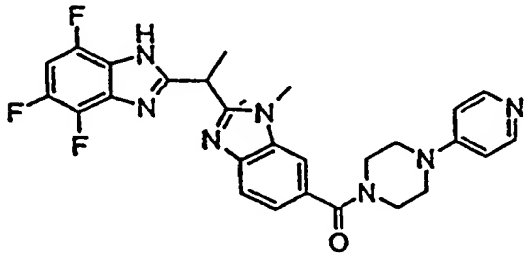
MS (FAB) $C_{28}H_{31}F_3N_6O$ m/e calc 524.6; found 525 (MH^+);

mp 173.2 - 176.8 °C;

Rf 0.08 (chloroform / methanol = 9/1).

Example 15

3-Methyl-5-[(4-pyridin-4-yl)piperazin-1-ylcarbonyl]-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(4-pyridinyl)piperazine (method B).

Yield:65% of theory, colorless solid.

^{1}H-NMR (300 MHz, DMSO-*d6*): 1.89 (d, 3H, J=7.1 Hz), 3.43 (br s, 4H), 3.65 (br s, 4H), 3.81 (s, 3H), 4.98 (q, 1H, J=7.1 Hz), 6.84 (d, 2H, J =6.5 Hz), 7.26-7.35 (m, 2H), 7.65 (d, 1H, J=8.3 Hz), 7.69 (s, 1H), 8.18 (d, 2H, J=6.5 Hz), 13.44 (br s, 1H);

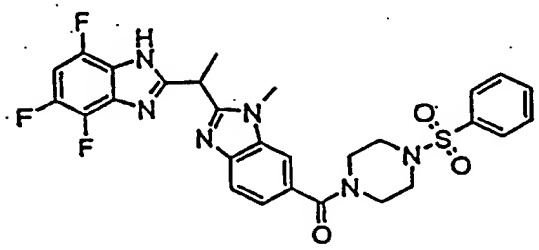
MS (FAB) $C_{27}H_{24}F_3N_7O$ m/e calc 519.5; found 520 (MH^+);

mp 220.8 - 222.9 °C;

Rf 0.15 (chloroform / methanol = 4/1).

Example 16

5-(4-Benzenesulfonylpiperazin-1-ylcarbonyl)-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and example 35A (method B).

Yield: 14.7% of theory, colorless powder

^{1}H-NMR (300 MHz, DMSO-*d6*) 1.85 (d, 3H, J=7.1 Hz), 2.97 (m, 4H), 3.59 (m, 4H), 3.76 (s, 3H), 4.95 (q, 1H, J=7.1 Hz), 7.16 (dd, 1H, J=1.3, 8.3 Hz), 7.25-7.35 (m, 1H), 7.55-7.60 (m, 2H), 7.64-7.78 (m, 5H), 13.45 (br s, 1H);

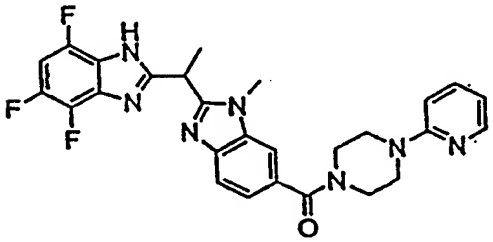
MS (FAB) $C_{28}H_{25}F_3N_6O_3S$ m/e calc 582.6; found 583 (MH^+);

mp >231.5 °C (dec.);

Rf 0.47(ethyl acetate / methanol = 20/3).

Example 17

3-Methyl-5-[4-(2-pyridyl)piperazin-1-ylcarbonyl]-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(2-pyridinyl)piperazine (method B).

Yield:26% of theory, colorless solid

^{1}H-NMR (300 MHz, CD_3OD): 1.18 (dd, 3H, J=7.2, 2.1 Hz), 2.61 - 3.20 (m. 8H), 3.04 (s, 3H), 4.19 (dq, 1H, J=7.1, 2.1 Hz), 5.90 (dd, 1H, J=5.2, 1.6 Hz), 6.04 (d, 1H, J=8.7 Hz), 6.17 - 6.26 (m, 1H), 6.57 (d, 1H, J=8.3 Hz), 6.74 - 6.80 (m, 1H), 6.86 (s, 1H), 6.92 (d, 1H, J=8.3 Hz), 7.28 - 7.30 (m, 1H);

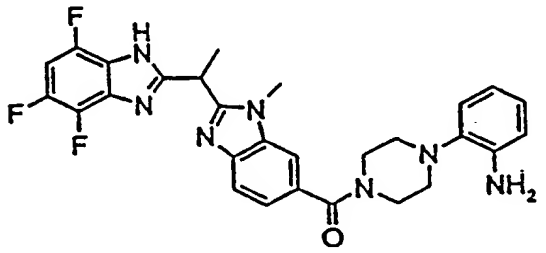
MS (FAB) $C_{27}H_{24}F_3N_7O$ m/e calc 519.5; found 520 (MH^+);

mp 250-252 °C (dec.);

Rf 0.19 (ethyl acetate / methanol = 9/1).

Example 18

5-[4-(2-Aminophenyl)piperazin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(2-aminophenyl)piperazine hydrochloride (method B).

Yield: 56% of theory, colorless solid.

^{1}H-NMR (300 MHz ,DMSO-d_6): 1.87 (d, 3H, J=7.1Hz), 2.81 (m, 4H), 3.29 (s, 4H), 3.81 (s, 3H), 4.81 (s, 2H), 4.97 (q, 1H, J=7.1 Hz) 6.53 (dt, 1H, J=7.6, 1.4 Hz), 6.67 (dd, 1H, J=7.8, 1.2 Hz), 6.79-6.84 (m, 1H), 6.90 (dd, 1H, J=7.8, 1.2 Hz), 7.25 (dd, 1H, J=8.2, 1.4 Hz), 7.26-7.30 (m, 1H), 7.63-7.67 (m, 2H), 13.46 (s, 1H);

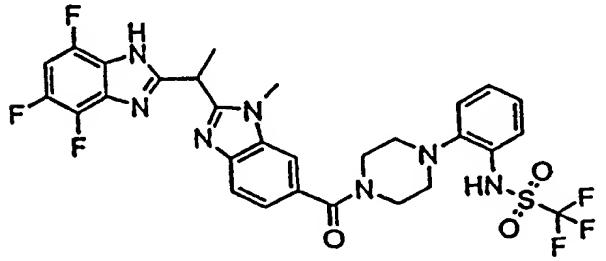
MS (FAB) $C_{28}H_{26}F_3N_7O$ m/e calc 533.5; found 534 (MH^+);

mp >250 °C;

Rf 0.37 (chloroform / methanol = 10/1).

Example 19

3-Methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-5-[4-[2-(trifluoromethanesulfonamido)phenyl]piperazin-1-ylcarbonyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(2-trifluoromethanesulfonamidephenyl)piperazine hydrochloride (method B).

Yield 23% of theory, colorless solid.

^{1}H-NMR (300 MHz , DMSO-d_6): 1.87 (d, 3H, J=7.1Hz), 2.98 (m, 4H), 3.57 (m, 4H), 3.82 (s, 3H), 5.00 (q, 1H, J=7.1 Hz), 7.12-7.18 (m, 1H), 7.28-7.35 (m, 5H), 7.65 (d, 1H, J=8.3 Hz), 7.71 (s, 1H);

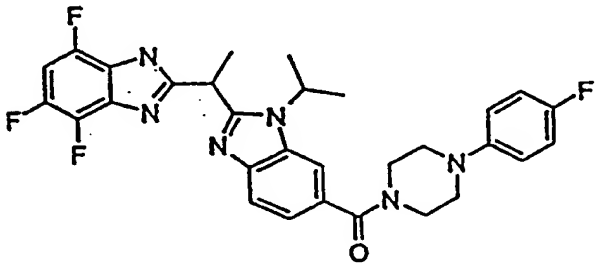
MS (FAB) $C_{29}H_{25}F_6N_7O_3S$ m/e calc 665.6; found 666 (MH^+);

mp 239-240 °C;

Rf 0.49 (chloroform / methanol = 10/1).

Example 20

5-[4-(4-Fluorophenyl)piperazin-1-ylcarbonyl]-3-isopropyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl-3*H*-benzimidazole



A mixture of example 8A (1.00 g, 3.67 mmol) and example 37A (1.38 g, 3.67 mmol) and DMPU (2 mL) was stirred under vacuum at 50°C for 1h to remove residual gases and heated to 190 °C for 16 hours. After cooled to room temperature, the mixture was diluted with ca.150 mL of ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate solution and brine, dried, and concentrated. Silica gel column chromatography (ethyl acetate eluent) followed by crystallization from chloroform / diisopropyl ether to afford a white solid, that was recrystallized from chloroform/n-hexane.

Yield 520 mg (24% of theory), colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.41 (d, 3H, J=6.8 Hz), 1.59 (d, 3H, J=6.8 Hz), 1.87 (d, 3H, J=7.0 Hz), 3.13 (br s, 4H), 3.66 (br s, 4H), 4.88 (quint, 1H, J=6.8 Hz), 5.01 (q, 1H, J=7.0 Hz), 6.94-7.09 (m, 4H), 7.23-7.35 (m, 2H), 7.67 (d, 1H, J=8.3 Hz), 7.76 (s, 1H), 13.46 (br s, 1H) ;

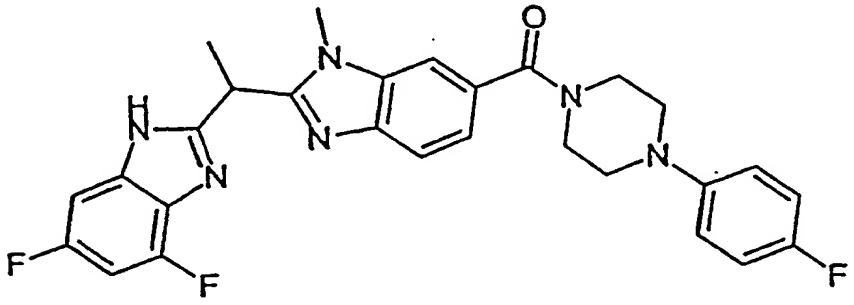
MS (FAB) $C_{30}H_{28}F_4N_6O$ m/e calc 564.6; found 565 (MH^+);

mp 154.8-155.8 °C;

Rf 0.15 (ethyl acetate).

Example 21

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)ethyl]-5-[4-(4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-(4-fluoro-phenyl)-piperazine (method B).

Yield: 75% of theory;

^{1}H-NMR (200 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 3.11 (cm, 4H), 3.65 (cm, 4H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.95-7.15 (m, 6H), 7.27 (dd, 1H, J=8 and 0.5 Hz), 7.66 (d, 1H, J=8Hz), 7.68 (d, 1H, J=0.5Hz), 12.8 and 13.1 (2 br s, 1H);

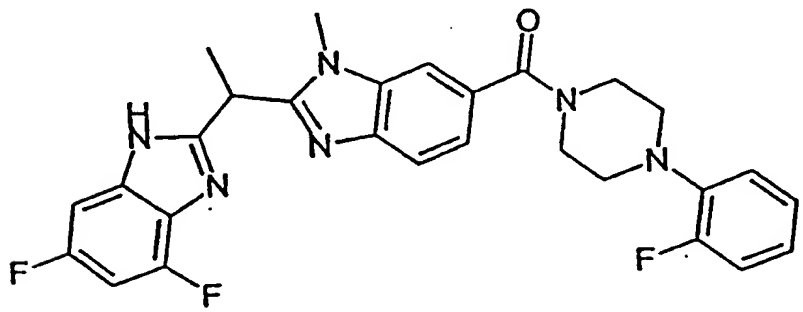
MS (EI) $C_{28}H_{25}F_3N_6O$ m/e calc 518.5; found 518 (M^+);

m.p. 150 155°C /dec.);

Rf 0.60 (dichloromethane / methanol = 10/1).

Example 22

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)ethyl]-5-[4-(2-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-(2-fluoro-phenyl)-piperazine (method B).

Yield: 92% of theory;

^{1}H-NMR (200 MHz, DMSO-d_6): 1.86 (d, 3H, J=7.1 Hz), 3.05 (cm, 4H), 3.70 (cm, 4H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.95-7.21 (m, 6H), 7.29 (dd, 1H, J=8 and 0.5 Hz), 7.67 (d, 1H, J=8Hz), 7.69 (d, 1H, J=0.5Hz), 12.9 (br s, 1H);

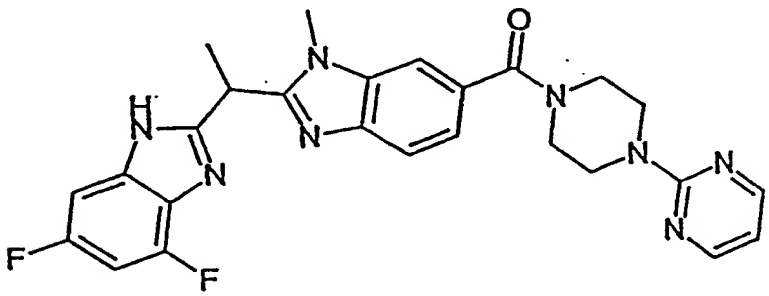
MS (DCI/NH_3) $C_{28}H_{23}F_3N_6O$ m/e calc 518.5; found 519 ($M+H^+$);

m.p. 150-160°C (dec.);

Rf 0.54 (dichloromethane / methanol = 10/1).

Example 23

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)ethyl]-3-methyl-5-[4-(2-pyrimidinyl)piperazin-1-ylcarbonyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-(2-pyrimidyl)piperazine (method B).

Yield: 44% of theory;

^{1}H-NMR (200 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 3.61 (cm, 4H), 3.80 (cm, 4H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.68 (t, 1H, J=5Hz) 6.95-7.21 (m, 2H), 7.29 (dd, 1H, J=8 and 0.5 Hz), 7.67 (d, 1H, J=8Hz), 7.69 (d, 1H, J=0.5Hz), 8.39 (d, 1H, J=5Hz),12.9 (br s, 1H);

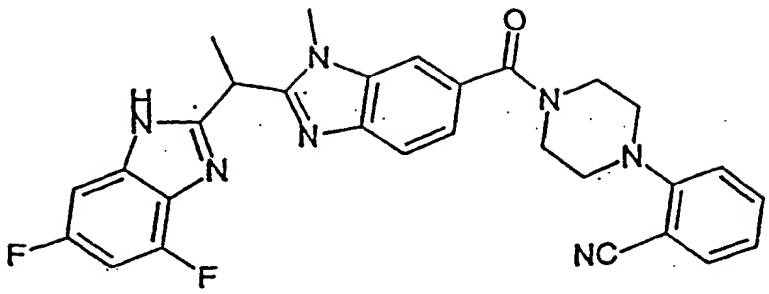
MS (DCI/NH_3) $C_{26}H_{24}F_2N_8O$ m/e calc 502.5; found 503 ($M+H^+$);

m.p. >200°C;

Rf 0.35 (dichloromethane / methanol = 10/1).

Example 24

5-[4-(2-Cyanophenyl)piperazin-1ylcarbonyl]-2-[1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-(2-cyano-phenyl)-piperazine (method B).

Yield: 77% of theory;

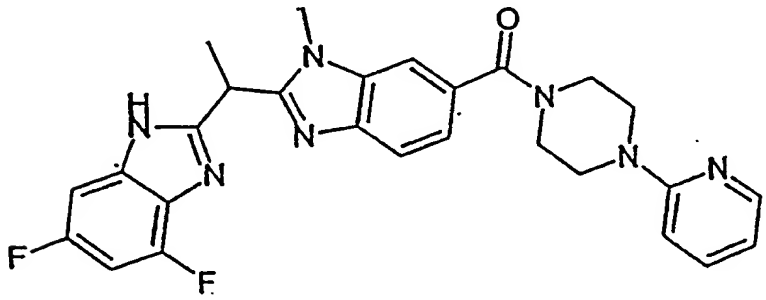
^{1}H-NMR (200 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 3.17 (cm, 4H), 3.71 (cm, 4H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.68 (t, 1H, J=5Hz) 6.95-7.25 (m, 4H), 7.29 (dd, 1H, J=8 and 0.5 Hz), 7.58-7.78 (m, 4H), 12.9 (br s, 1H);

MS (ESI) $C_{29}H_{25}F_2N_7O$ m/e calc 502.5; found 526.6 ($M+H^+$);

Rf 0.38 (ethyl acetate / ethanol = 20/1).

Example 25

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)ethyl]-5-[4-(2-pyridinyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-(2-pyridyl)piperazine (method B).

Yield: 47% of theory;

^{1}H-NMR (200 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 3.58 (cm, 8H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.67 (dd, 1H, J=9 and 5Hz) 6.85 (d, 1H, J=9Hz), 6.94-7.21 (m, 2H), 7.29 (dd,

1H, J=8 and 0.5 Hz), 7.58 (dt, 1H, J= 9 and 1 Hz), 7.67 (d, 1H, J=8Hz), 7.69 (d, 1H, J=0.5Hz), 8.12 (dd, 1H, J=5 and 1Hz), 12.9 (br s, 1H);

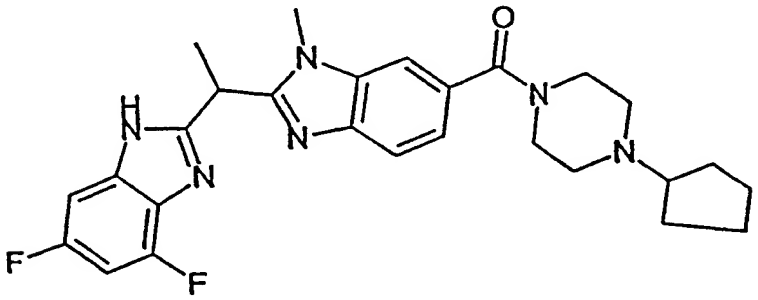
MS (ESI) $C_{27}H_{25}F_2N_7O$ m/e calc 501.5; found 502.4 ($M+H^+$);

m.p. 316°C;

Rf 0.34 (ethyl acetate / ethanol = 20/3).

Example 26

5-[4-(Cyclopentyl)piperazin-1ylcarbonyl]-2-[1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-cyclopentyl-piperazine (method B).

Yield: 54% of theory;

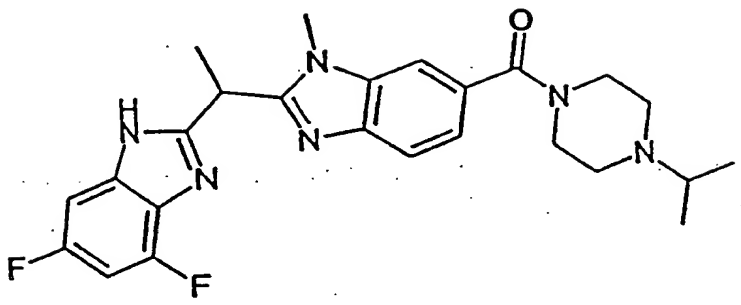
^{1}H-NMR (200 MHz, DMSO-d_6): 1.21-190 (m, 8H), 1.88 (d, 3H, J=7.1 Hz), 1.95 (cm, 4H), 3.30-3.65 (m, 5H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.94-7.21 (m, 3H), 7.52 (s, 1H), 7.55 (d, 1H, J=8Hz), 12.9 (br s, 1H);

MS (DCI/NH_3) $C_{27}H_{30}F_2N_6O$ m/e calc 492.6; found 493 ($M+H^+$);

Rf 0.85 (dichloromethane / ethanol = 5/1).

Example 27

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)ethyl]-5-[4-(isopropyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-isopropylpiperazine (method B).

Yield: 69% of theory;

^{1}H-NMR (200 MHz, DMSO-d_6): 0.96 (d, 6H, J=7Hz), 1.85 (d, 3H, J=7.1 Hz), 2.44 (cm, 4H), 2.68 (h, 1H, J=7Hz), 3.50 (cm, 4H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.95-7.25 (m, 3H), 7.52 (s, 1H), 7.55 (d, 1H, J=8Hz), 12.9 (br s, 1H);

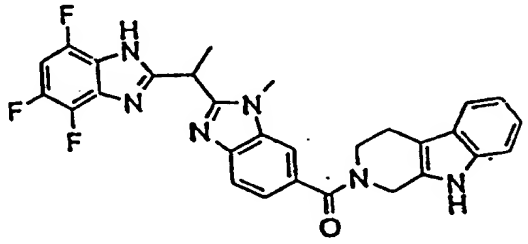
MS (DCI/NH_3) $C_{25}H_{28}F_2N_6O$ m/e calc 466.5; found 467 ($M+H^+$);

m.p. 250°C;

Rf 0.43 (dichloromethane / methanol = 10/1).

Example 28

3-Methyl-5-(1,2,3,4-tetrahydro-9*H*-prido[3,4-*b*]indol-2-ylcarbonyl)-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1,2,3,4-tetrahydro-9*H*-prido[3,4-*b*]indole (method B).

Yield: 66% of theory;

^{1}H-NMR (300 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.1 Hz), 2.73-2.82 (m, 2H), 3.57-4.04 (m, 2H), 3.81 (s, 3H), 4.65-4.90 (m, 2H), 4.98 (q, 1H, J=7.1 Hz), 6.94-7.07 (m, 2H), 7.21-7.42 (m, 4H), 7.68 (d, 1H, J=8.2 Hz), 7.71 (d, 1H, J=0.5 Hz), 10.90 (br s, 1H), 13.48 (br s, 1H);

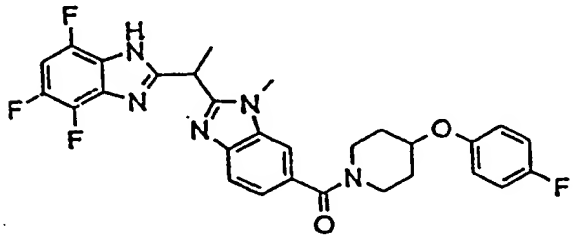
MS (FAB) $C_{29}H_{23}F_3N_6O$ m/e calc 528.5; found 529 (MH^+);

mp 199 °C (dec.);

Rf 0.63 (ethyl acetate / methanol = 9/1).

Example 29

5-[4-(4-Fluorophenoxy)piperidin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 1-(4-fluoro-phenoxy)piperazine (method B).

Yield: 68% of theory, colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.64 (m, 2H), 1.86 (d, 3H, J=7.1 Hz), 1.94 (m, 2H), 3.35-3.40 (m, 2H), 3.57-4.36 (m, 2H), 3.80 (s, 3H), 4.58-4.60 (m, 1H), 4.97 (q, 1H, J=7.1 Hz), 6.98-7.04 (m, 2H), 7.07-7.14 (m, 2H), 7.23 (dd, 1H, J=1.4, 8.3 Hz), 7.27-7.34 (m, 1H), 7.62 (d, 1H, J= 8.3 Hz), 7.65 (s 1H), 13.45 (br s, 1H);

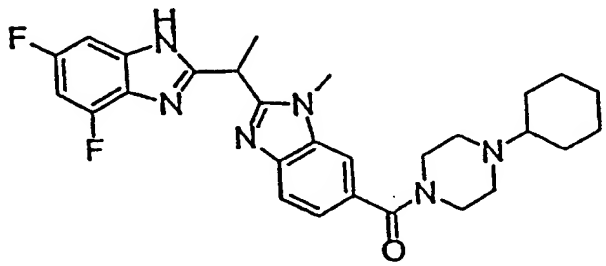
MS (FAB) $C_{29}H_{25}F_4N_5O_2$ m/e calc 551.5; found 552 (MH^+);

mp 151.6 □C (dec.);

Rf 0.34 (ethyl acetate / methanol = 10/1).

Example 30

5-[4-(Cyclohexyl)piperazin-1-ylcarbonyl]-2-[1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-cyclohexylpiperazine (method B).

Yield: 51% of theory;

^{1}H-NMR (200 MHz, DMSO-d_6): 0.95-1.30 (m, 5H), 1.50-1.90 (m, 5H), 1.88(d, 3H, J=7.1 Hz), 2.16-2.60 (cm, 4H), 3.25-3.65 (m, 5H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.95-7.25 (m, 3H), 7.52 (s, 1H), 7.55 (d, 1H, J=8Hz), 12.9 (br s, 1H);

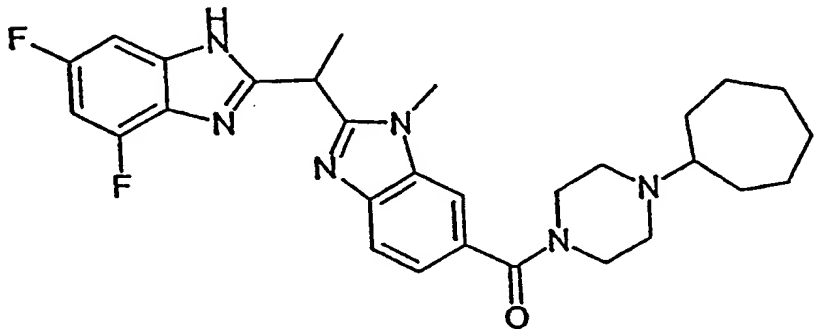
MS (ESI) $C_{28}H_{32}F_2N_6O$ m/e calc 492.6; found 506.6 ($M+H^+$);

m.p.: 215-217°C

Rf 0.71 (dichloromethane / ethanol = 20/3).

Example 31

5-[4-(Cycloheptyl)piperazin-1-ylcarbonyl]-2-[1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 1-cycloheptylpiperazine (method B).

Yield: 33% of theory;

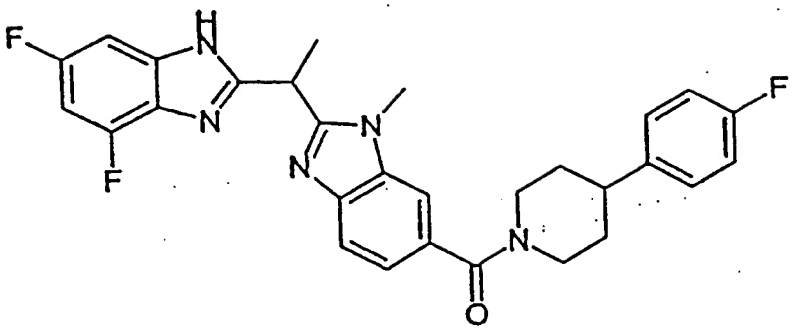
^{1}H-NMR (200 MHz, DMSO-d_6): 1.12-1.90 (m, 12H), 1.88 (d, 3H, J=7.1 Hz), 2.35-2.60 (m, 4H), 3.25-3.65 (m, 5H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.94-7.22 (m, 3H), 7.62 (s, 1H), 7.65 (d, 1H, J=8Hz), 12.8 (br s, 1H);

MS (DCI/NH_3) $C_{29}H_{34}F_2N_6O$ m/e calc 520.6; found 521 ($M+H^+$);

m.p.: 202-203°C

Example 32

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-5-[4-(4-fluorophenyl)piperidin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and 4-(4-fluorophenyl)piperidine (J.Med. Chem. 38, 1995, 2004; method B).

Yield: 51% of theory;

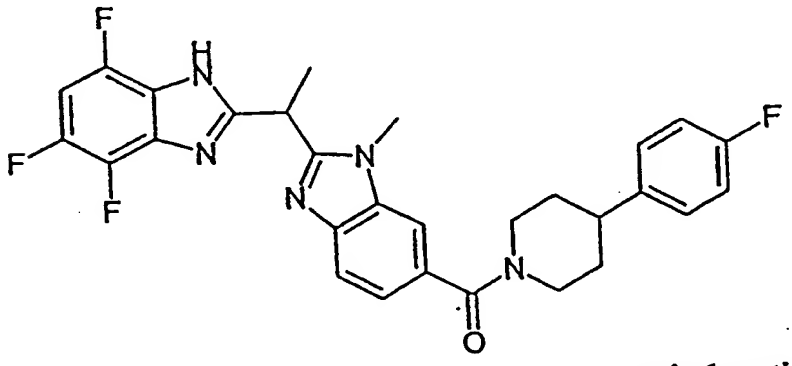
^{1}H-NMR (200 MHz, DMSO-d_6): 1.55-1.90 (m, 4H), 1.88 (d, 3H, J=7.1 Hz), 2.70-3.30 (m, 3H), 3.81 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 6.92-7.40 (m, 7H), 7.64 (d, 1H, J=8Hz), 7.68 (s, 1H), 12.8 (br s, 1H);

MS (ESI) $C_{29}H_{26}F_3N_5O$ m/e calc 517.6; found 518.4 ($M+H^+$);

m.p. 240°C

Example 33

5-[4-(4-Fluorophenyl)piperidin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and 4-(4-fluorophenyl)piperidine (J.Med. Chem. 38, 1995, 2004; method B).

Yield: 37% of theory;

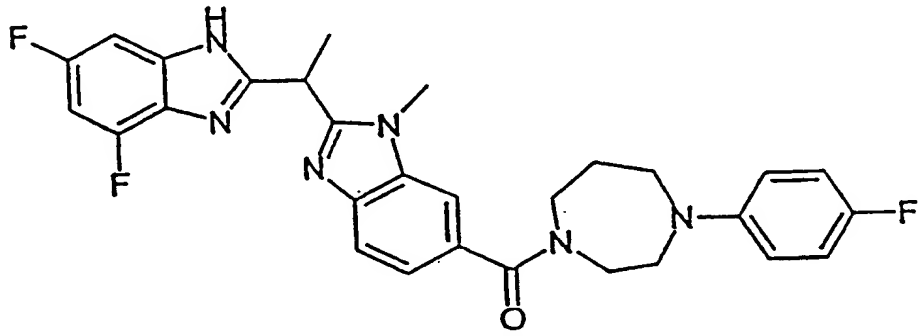
^{1}H-NMR (200 MHz, DMSO-d_6): 1.55-1.90 (m, 4H), 1.88 (d, 3H, J=7.1 Hz), 2.70-3.20 (m, 3H), 3.82 (s, 3H), 4.97 (q, 1H, J=7.1 Hz), 7.08-7.40 (m, 6H), 7.64 (d, 1H, J=8Hz), 7.68 (s, 1H), 13.5 (br s, 1H);

MS (ESI) $C_{29}H_{25}F_4N_5O$ m/e calc 535.5; found 536.4 ($M+H^+$);

m.p. 230°C.

Example 34

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-5-[4-(4-fluorophenyl)1,4-diazacyclohept-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 12A and example 33A (method B).

Yield: 21% of theory;

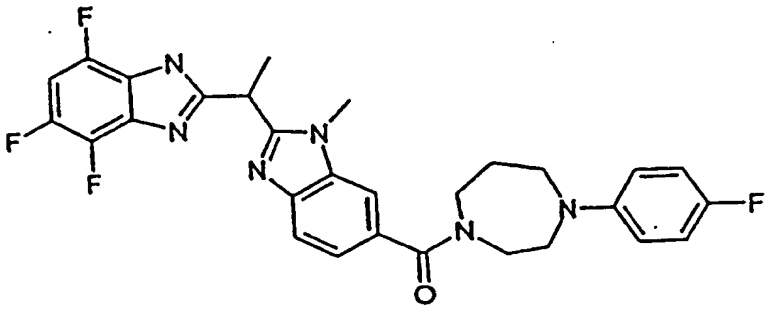
^{1}H-NMR (200 MHz, DMSO-d_6): 1.55-2.05 (m, 2H), 1.85 (d, 3H, J=7.1 Hz), 3.20-3.85 (m, 11H), 4.95 (q, 1H, J=7.1 Hz), 6.55-7.20 (m, 9H), 7.50 (cm, 1H), 12.9 (br s, 1H);

MS (ESI) $C_{29}H_{27}F_3N_6O$ m/e calc 532.6; found 533.3 ($M+H^+$);

m.p. 235-238°C.

Example 35

5-[4-(4-Fluorophenyl)-1,4-diazacyclohept-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 11A and example 33A (method B).

Yield: 14% of theory;

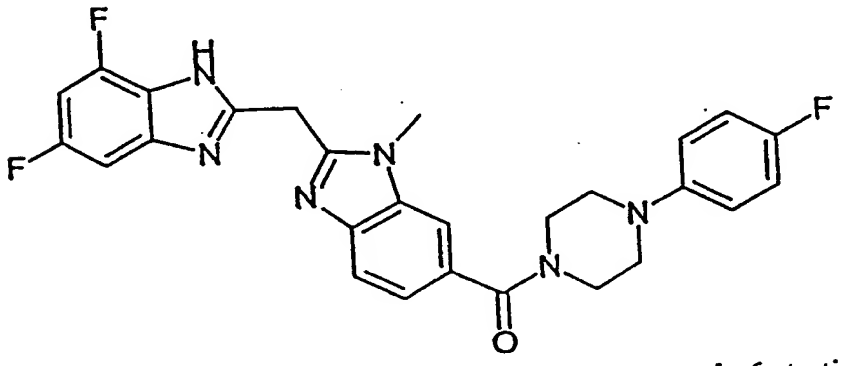
^{1}H-NMR (200 MHz, DMSO-d_6): 1.55-2.05 (m, 2H), 1.85 (d, 3H, J=7.1 Hz), 3.20-3.85 (m, 11H), 4.95 (q, 1H, J=7.1 Hz), 6.55-7.10 (m, 6H), 7.25 (cm, 1H), 7.42-7.65 (m, 1H), 13.5 (br s, 1H);

MS (ESI) $C_{29}H_{26}F_4N_6O$ m/e calc 550.6; found 551.3 ($M+H^+$);

m.p. >250°C.

Example 36

2-[(4,6-Difluoro-1H-benzimidazol-2-yl)methyl]-5-[4-(4-fluorophenyl)piperazin-1ylcarbonyl]-3-methyl-3H-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 14A and 1-(4-fluorophenyl)piperazine (method B).

Yield: 41% of theory;

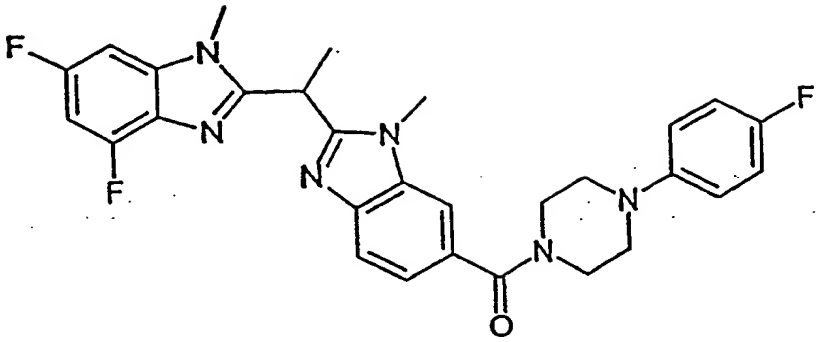
^{1}H-NMR (200 MHz, DMSO-d_6): 3.11 (cm, 4H), 3.65 (cm, 4H), 3.88 (s, 3H), 4.62 (s, 2H), 6.95-7.50 (m, 7H), 7.62 (d, 1H, J=8Hz), 7.68 (d, 1H, J=0.5Hz), 12.9 and 13.1 (2 br.s, 1H);

MS (DCI/NH_3) $C_{27}H_{23}F_3N_6O$ m/e calc 504.5; found 505 ($M+H^+$);

m.p. 195°C ;

Example 37

2-[1-(4,6-Difluoro-1-methyl-1*H*-benzimidazol-2-yl)ethyl]-5-[4-(4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 30A and 1-(4-fluorophenyl)piperazine (method B).

Yield: 53% of theory;

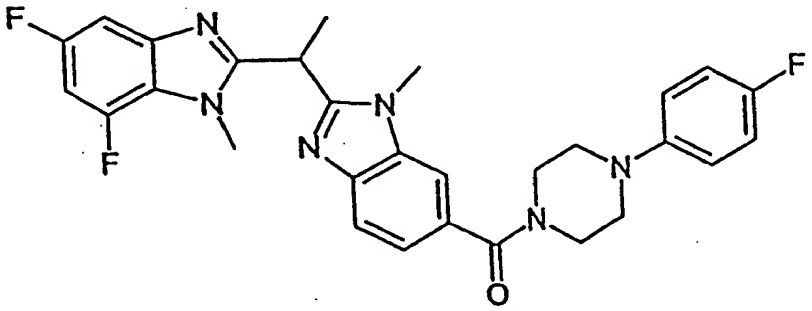
^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (d, 3H, J=7Hz), 3.12 (cm, 4H), 3.63 (s,3H), 3.65 (cm, 4H), 3.78 (s, 3H), 5.12 (q, 1H, J=7Hz), 6.92-7.15 (m, 5H), 7.26 (dd; 1H, J=8 and 0.5Hz), 7.38 (dd, 1H, J=8 and 1Hz), 7.62 (d, 1H, J=8Hz), 7.68 (d, 1H, J=0.5Hz);

MS (DCI/NH_3) $C_{29}H_{27}F_3N_6O$ m/e calc 532.6; found 533 ($M+H^+$);

R_f 0.23 (dichloromethane/ethanol = 20:1).

Example 38

2-[1-(4,6-Difluoro-3-methyl-3*H*-benzimidazol-2-yl)methyl]-5-[4-(4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-3*H*-benzimidazole



The preparation was carried out in analogy to example 6 starting from example 31A and 1-(4-fluoro-phenyl)-piperazine (method B).

Yield: 72% of theory;

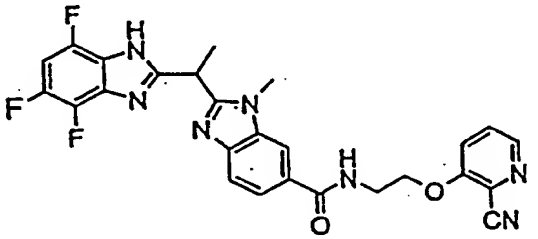
^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (d, 3H, J=7Hz), 3.12 (cm, 4H), 3.67 (cm, 4H), 3.72 (s,3H), 3.82 (s, 3H), 5.12 (q, 1H, J=7Hz), 6.92-7.35 (m, 7H), 7.64 (d, 1H, J=8Hz), 7.69 (d, 1H, J=0.5Hz);

MS (ESI) $C_{29}H_{27}F_3N_6O$ m/e calc 532.6; found 533.3 ($M+H^+$);

m.p. 230-232°C

Example 39

N-[2-[(2-Cyanopyridin-3-yl)oxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



A solution of example 11A (161.7 mg, 0.432 mmol, 1.0 eq.), example 55A (102 mg, 0.432 mmol, 1.0 eq.), 1-hydroxybenzotriazole (90 mg, 0.666 mmol, 1.5 eq N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (100 mg, 0.522 mmol, 1.2 eq.) and *N,N*-diisopropylethylamine (0.15 mL, 0.864 mmol, 2.0 eq.) in *N,N*-dimethylformamide (10 mL) was stirred at room temperature for 1 day. The solvent was evaporated in vacuo and the residue was dissolved in water and extracted into ethyl acetate. The ethyl acetate layer was washed by 5% $NaHCO_3$ aq. and sat. NaCl aq., dried over Na_2SO_4, filtrated and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate / methanol = 20/1 as eluent) and recrystallization (ethyl acetate / diethyl ether = 1/2) afforded colorless powder.

Yield: 116.8 mg (52% of theory), colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.87 (d, 3H, J=7.0 Hz), 3.68-3.71 (m, 2H), 3.81 (s, 3H), 4.42 (t, 2H, J=5.8 Hz), 4.98 (q, 1H, J=7.0 Hz), 7.29 (m, 1H), 7.63 (d, 1H, J=8.4 Hz), 7.68-7.72 (m, 2H), 7.90 (d, 1H, J=8.8 Hz), 8.07 (s, 1H), 8.30 (d, 1H, J=4.5 Hz), 8.69 (m, 1H), 13.48 (br s, 1H);

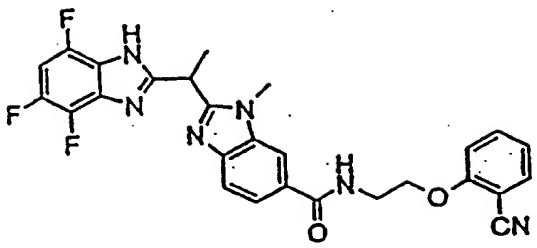
MS (FAB) $C_{26}H_{20}F_3N_7O_2$ m/e calc 519.5; found 520 (MH^+);

mp 239.7 °C (dec.);

Rf 0.58 (ethyl acetate / methanol = 9/1)

Example 40

N-[2-[(2-Cyanophenyl-1-oxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 20A.

Yield 43% of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.88 (d, 3H, J=7.2 Hz), 3.91 (s, 3H), 4.00 (q, 2H, J=5.32 Hz), 4.31 (t, 2H, J=5.0 Hz), 4.91 (q, 1H, J=5.3 Hz), 6.86-6.94 (m, 2H), 7.01-7.08 (m, 2H), 7.53-7.60 (m, 2H), 7.78 (s, 2H), 7.98 (s, 1H), 11.99 (br s, 1H);

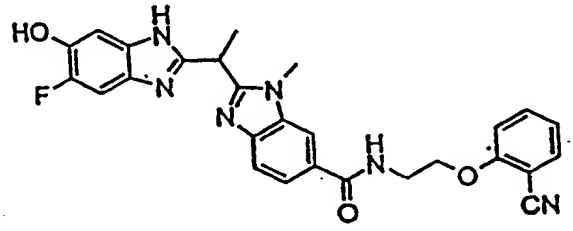
MS (FAB) $C_{27}H_{21}F_3N_6O_2$ m/e calc 518.5; found 519 (MH^+);

mp 150 °C;

Rf 0.70 (chloroform / methanol = 10/1)

Example 41

N-[2-[(2-Cyanophenyl-1-oxy]ethyl]-2-[1-(5-fluoro-6-hydroxy-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 66A and example 20A.

Yield 47% of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.82 (d, 3H, J=7.1 Hz), 3.69 (q, 2H, J=6.1 Hz), 4.34 (t, 2H, J=6.1 Hz), 4.87 (q, 1H, J=7.0 Hz), 6.93 (d, 1H, J=8.1 Hz), 7.02-7.17 (m, 2H), 7.27 (d, 1H, J=11.6 Hz), 7.35 (d, 1H, J=8.5 Hz), 7.62-7.68 (m, 2H), 7.69-7.74 (m, 2H), 8.06 (s, 1H), 8.66 (t, 1H, J=5.3 Hz), 12.06 (s, 1H);

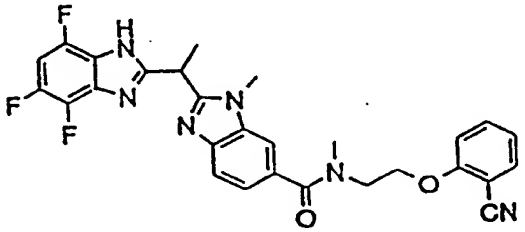
MS (FAB) $C_{27}H_{23}FN_6O_3$ m/e calc 498.5; found 499 (MH^+);

mp 190 °C;

Rf 0.53 (chloroform / methanol = 10/1).

Example 42

N-[2-[(2-Cyanophenyl-1-oxy]ethyl]-*N*-methyl-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 49A.

Yield 56% of theory, colorless powder..

^{1}H-NMR (300 MHz, DMSO-d_6): 1.86 (d, 3H, J=7.1 Hz), 3.10 (s, 3H), 3.64-3.79 (m, 2H), 3.79 (s, 3H), 4.40 (m, 2H), 4.96 (q, 1H, J=7.1 Hz), 7.08 (m, 1H), 7.23 (dd, 1H, J=1.3, 8.2 Hz), 7.26-7.34 (m, 2H), 7.58-7.70 (m, 1H), 7.60 (d, 1H, J=8.2 Hz), 7.63 (s, 1H), 7.72 (d, 1H, J=7.3 Hz), 13.44 (br s, 1H);

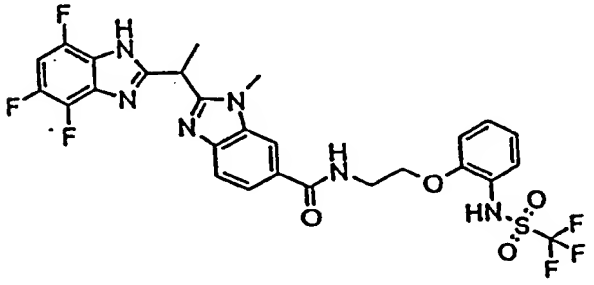
MS (FAB) $C_{28}H_{23}F_3N_6O_2$ m/e calc 532.5; found 533 (MH^+);

mp 231.3-231.7 °C;

Rf 0.50 (ethyl acetate / methanol = 10/1).

Example 43

3-Methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(2-trifluoromethanesulfonylaminophenoxy)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 53A.

Yield: 41% of theory, colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 1.98 (d, 1H, J=7.2 Hz), 3.70 (s, 3H), 3.82-3.88 (m, 2H), 4.22 (t, 2H, J=4.7 Hz), 4.96 (q, 1H, J=7.2 Hz), 6.83-6.98 (m, 4H), 7.01 (dd, 1H, J=1.2, 8.0 Hz), 7.21-7.27 (m, 1H), 7.31 (dd, 1H, J=1.2, 8.5 Hz), 7.48 (dd, 1H, J=1.5, 8.0 Hz), 7.71 (s, 1H);

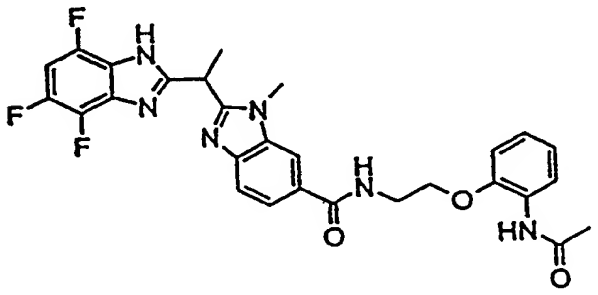
MS (FAB) $C_{27}H_{22}F_6N_6O_4S$ m/e calc 640.6; found 641 (MH^+);

mp 156-161 °C;

Rf 0.32 (chloroform / methanol = 9/1).

Example 44

N-[2-(2-*N*-Acetylaminophenoxy)ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 39A.

Yield: 20%of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-*d6*): 1.86 (d, 3H, J=7.1 Hz), 3.17 (d, 3H, J=5.3 Hz), 3.75 (q, 2H, J=5.6 Hz), 3.81 (s, 3H), 4.16 (t, 2H, J=5.4 Hz), 4.98 (q, 1H, J=7.1 Hz), 6.84-6.89 (m, 1H), 7.00-7.06 (m, 2H), 7.28-7.29 (m, 1H), 7.63 (d, 1H, J=8.5 Hz), 7.76 (d, 1H, J=8.5 Hz), 8.04 (d, 1H, J= 7.9Hz), 8.10 (s, 1H), 8.72 (t, 1H, J= 5.8Hz), 8.94 (s, 1H), 13.46 (br s, 1H);

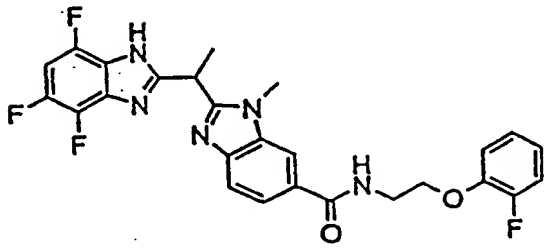
MS (FAB) $C_{28}H_{23}F_3N_6O_3$ m/e calc 550.5; found 551 (MH^+);

mp 179.1-180.0 °C;

Rf 0.40 (chloroform / methanol = 10/1).

Example 45

N-[2-[(2-Fluoro-phenyl-1-oxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 76A.

Yield: 30% of theory, colorless powder.

^{1}H NMR (300 MHz, DMSO-d_6):1.86 (d, 3H, J=7.1 Hz), 3.67 (q, 2H, J=6.0 Hz), 3.82 (s, 3H), 4.23 (t, 2H, J=6.0 Hz), 5.00 (q, 1H, J=7.1 Hz), 6.91-6.97 (m, 1H), 7.09-7.30 (m, 4H), 7.63 (d, 1H, J=8.5 Hz), 7.74 (dd, 1H, J=8.5, 1.5 Hz), 8.11 (d, 1H, J=1.0 Hz), 8.68 (t, 1H, J=5.5 Hz), 13.47 (br s, 1H);

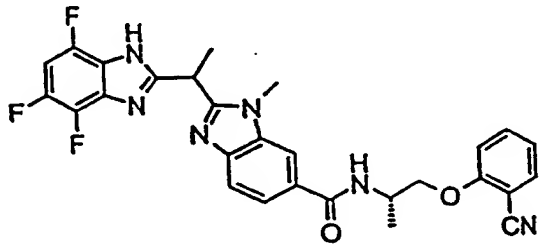
MS (FAB) $C_{26}H_{21}F_4N_5O_2$ m/e calc 511.5; found 512 (MH^+);

mp 240 °C.

Rf 0.43 (chloroform / methanol = 10/1).

Example 46

(S)-*N*-[2-[3-(2-Cyanophenyl-1-oxy]propyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 60A.

Yield: 48% of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.34 (d, 3H, J=6.7 Hz), 1.88 (d, 3H, J=7.1 Hz), 3.83 (s, 3H), 4.15 (dd, 1H, J=9.7, 6.6 Hz), 4.29 (dd, 1H, J=9.7, 6.1 Hz), 4.38-4.47 (m, 1H), 5.00 (q, 1H,

J=7.1 Hz), 7.09 (t, 1H, J=7.6 Hz), 7.26-7.35 (m, 1H), 7.38 (d, 1H, J=8.6 Hz), 7.61-7.76 (m, 4H), 8.08 (s, 1H), 8.39 (d, 1H, J=7.4 Hz), 13.48 (br s, 1H);

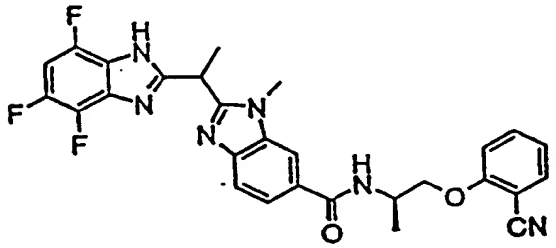
MS (FAB) $C_{28}H_{23}F_3N_6O_2$ m/e calc 532.5; found 533 (MH^+);

mp 252.4 - 253.6 °C

Rf 0.25 (chloroform / methanol = 1/19).

Example 47

(R)-N-[2-[3-(2-Cyanophenyl-1-oxy]propyl]-3-methyl-2-[1-(4,5,7-trifluoro-1H-benzimidazol-2-yl)ethyl]-3H-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 61A.

Yield: 49% of theory, colorless powder.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.34 (d, 3H, J=6.7 Hz), 1.88 (d, 3H, J=7.1 Hz), 3.82 (s, 3H), 4.14 (dd, 1H, J=9.8, 6.6 Hz), 4.29 (dd, 1H, J=9.8, 6.1 Hz), 4.37-4.47 (m, 1H), 5.00 (q, 1H, J=7.1 Hz), 7.09 (t, 1H, J=7.6 Hz), 7.26-7.35 (m, 1H), 7.37 (d, 1H, J=8.6 Hz), 7.61-7.76 (m, 4H), 8.08 (s, 1H), 8.39 (d, 1H, J=7.4 Hz), 13.49 (br s, 1H);

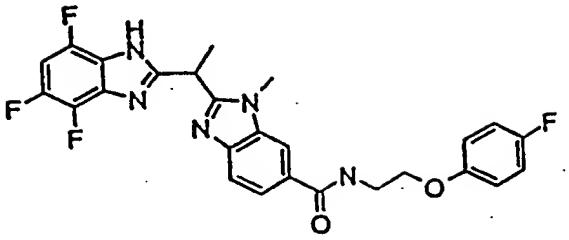
MS (FAB) $C_{28}H_{23}F_3N_6O_2$ m/e calc 532.5; found 533 (MH^+);

mp 250.5-252.0 °C.

Rf 0.25 (chloroform / methanol = 1/19).

Example 48

N-[2-[(4-Fluoro-phenyl-1-oxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 18A.

Yield: 44% of theory, colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.86 (d, 3H, J=7.1 Hz), 3.65 (q, 2H, J=5.9 Hz), 3.81 (s, 3H), 4.12 (t, 2H, J=5.9 Hz), 4.98 (q, 1H, J=7.1 Hz), 6.96-7.02 (m, 2H), 7.08-7.13 (m, 2H), 7.25-7.30 (m, 1H), 7.61 (d, 1H, J=8.4 Hz), 7.74 (dd, 1H, J=5.3 Hz), 8.10 (s, 1H), 8.65 (t, 1H, J=5.3 Hz), 13.43-13.45 (br s, 1H);

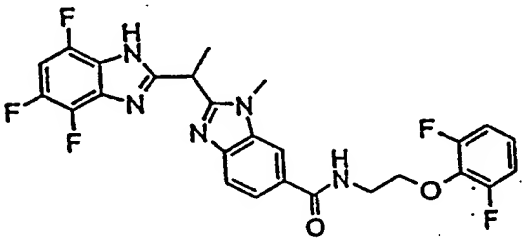
MS (FAB) $C_{26}H_{21}F_4N_5O_2$ m/e calc 509.5; found 510 (MH^+);

mp 126-130 °C.

Rf 0.20 (chloroform / methanol = 10/1).

Example 49

N-[2-[(2,4-Diluoro-phenyl-1-oxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 74A.

Yield: 14% of theory, colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.87 (d, 3H, J=7.1 Hz), 3.64 (q, 2H, J=5.6 Hz), 3.81 (s, 3H), 4.25 (t, 2H, J=5.9 Hz), 4.98 (q, 1H, J=7.1 Hz), 7.09-7.16 (m, 3H), 7.24-7.34 (m, 1H), 7.62 (d, 1H, J=8.4 Hz), 7.72 (dd, 1H, J=8.4, 1.4 Hz), 8.07 (d, 1H, J=1.0 Hz), 8.62 (t, 1H, J=5.4 Hz), 13.46 (s, 1H);

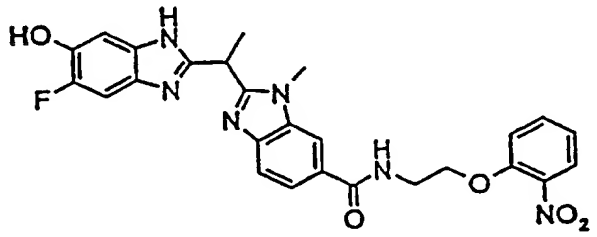
MS (FAB) $C_{26}H_{20}F_5N_5O_2$ m/e calc 529.5; found 530 (MH^+);

mp 158 °C.

Rf 0.46 (chloroform / methanol = 10/1).

Example 50

2-[1-(5-Fluoro-6-hydroxy-1*H*-benzoimidazol-2-yl)ethyl]-3-methyl-*N*-[2-(2-nitrophenoxy)ethyl]-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 50A and example 19A.

Yield: 27% of theory, pale yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.83 (d, 3H, J=7.1 Hz), 3.63-3.70 (m, 2H), 3.79 (s, 3H), 4.34 (t, 2H, J=5.9 Hz), 4.89 (q, 1H, J=7.1 Hz), 6.99 (d, 1H, J=8.1 Hz), 7.08-7.15 (m, 1H), 7.26 (d,1H, J=11.3 Hz), 7.45 (d, 1H, J=8.2 Hz), 7.61-7.68 (m, 1H), 7.72 (dd, 1H, J=1.4, 8.5 Hz), 7.85 (dd, 1H, J=1.6, 8.1 Hz), 8.05 (s, 1H), 8.59 (br t, 1H, J=5.4 Hz), 8.43 (br s, 1H);

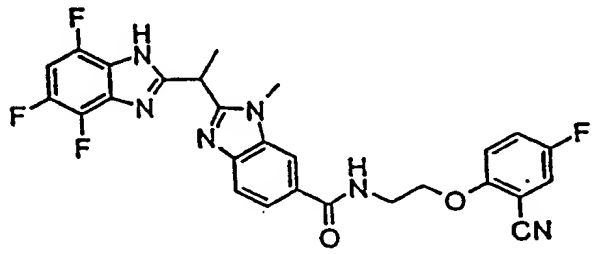
MS (FAB) $C_{26}H_{23}FN_6O_5$ m/e calc 518.5; found 519 (MH^+);

mp 165-173 °C;

Rf 0.38 (chloroform / methanol = 9/1).

Example 51

N-[2-(2-Cyano-4-fluoro-phenoxy)ethyl]-2-[1-(5-fluoro-6-hydroxy-1*H*-benzoimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazole-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 11A and example 62A.

Yield: 45% of theory.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.87 (d, 3H, J=7.1 Hz), 3.68 (q, 2H, J=5.5 Hz), 3.82 (s, 3H), 4.33 (t, 2H, J=5.9 Hz), 4.99 (q, 1H, J=7.0 Hz), 7.29-7.37 (m, 1H), 7.09 (d, 1H, J=4.2 Hz), 7.52-7.64 (m, 2H), 7.73 (d, 2H, J=8.1 Hz), 8.09 (s, 1H), 8.66 (t, 1H, J=5.3 Hz), 13.47 (s, 1H);

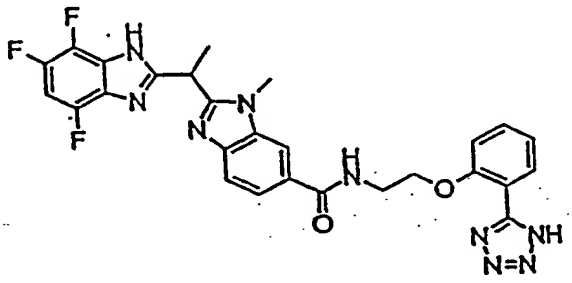
MS (FAB) $C_{27}H_{20}F_4N_6O_2$ m/e calc 536.5; found 537 (MH^+);

mp 148 °C;

Rf 0.64 (chloroform / methanol = 10/1).

Example 52

3-Methyl-*N*-{2-[2-(1*H*-tetrazol-5-yl)phenoxy]ethyl}-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide



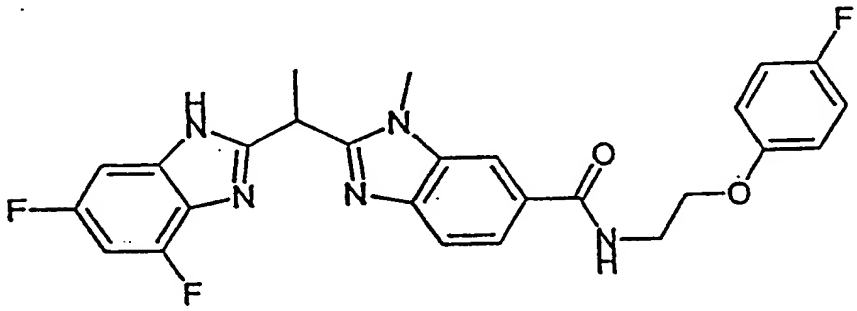
To a solution comprising a mixture of *N*-[2-[2-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide and *N*-[2-[2-(2-cyanoethylcarbamoyl)phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide (emaple 45A, 0.470 g) in methylene chloride (6.0 mL) was added 1,8-diazabicyclo[5.4.0]-7-undecene (0.457 mL, 3.06 mmol). The mixture was stirred at room temperature for 5 hours, and then trifluoroacetic acid (0.236 mL, 3.06 mmol) was added. After stirred for 10 minutes, the mixture was diluted with ethyl acetate, washed successively with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (chloroform / methanol = from 3/97 to 8/92 as eluent) to give 3-methyl-*N*-{2-[2-(1*H*-tetrazol-5-yl)phenoxy]ethyl}-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide (0.183 g) as colorless solid and *N*-[2-[2-(2-cyanoethylcarbamoyl)phenoxy]ethyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole-5-carboxamide (0.192 g) as colorless solid.

Yield 0.183 g (41% of theory), colorless solid.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.86 (d, 1H, J=7.1 Hz), 3.81 (s, 3H), 3.81-3.87 (m, 2H), 4.38 (t, 2H, J=5.2 Hz), 4.99 (q, 1H, J=7.1 Hz), 7.14-7.19 (m, 1H), 7.22-7.31 (m, 1H), 7.37 (d, 1H, J=8.3 Hz), 7.54-7.60 (m, 1H), 7.64 (d, 1H, J=8.4 Hz), 7.75 (dd, 1H, J=1.5, 8.5 Hz), 8.10 (s, 1H), 8.15 (dd, 1H, J=1.7, 7.8 Hz), 9.00 (br s, 1H), 13.46 (br s, 1H), 15.75 (br s, 1H);
MS (FAB) $C_{27}H_{22}F_3N_9O_2$ m/e calc 561.5 found 562 (MH^+);
mp 203-206 °C;
Rf 0.25 (chloroform / methanol = 9/1).

Example 53

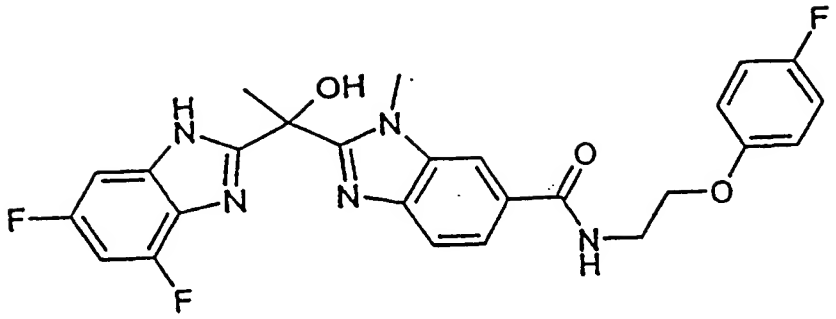
2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 12A and example 18A.
Yield: 59% of theory.
^{1}H-NMR (200 MHz, DMSO-d_6): 1.88 (d, 3H, J=7 Hz), 3.68 (q, 2H, J=6Hz), 3.81 (s, 3H), 4.12 (t, 2H, J=6 Hz), 4.98 (q, 1H, J=7 Hz), 6.94-7.12 (m, 6H), 7.64 (d, 1H, J=8 Hz), 7.76 (dd, 1H, J=5 and 0.5 Hz), 8.10 (d, 1H, J=0.5Hz), 8.70 (t, 1H, J=6 Hz), 12.9 (br s, 1H);
MS (DCI/NH_3) $C_{26}H_{22}F_3N_5O_2$ m/e calc 493.5; found 493 (MH^+);
mp 164 °C (dec.).
Rf 0.48 (dichloromethane / methanol = 10/1).

Example 54

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2yl)-1-hydroxy-ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



To a solution of sodium-meta-periodate (1.47g; 6.89mmol) in water (20ml) was added at room temperature a solution of example 53 (0.68g; 1.38mmol) in THF (20ml), followed by $RuCl_3$ (10mg) and stirring was continued for 5 days. After addition of isopropanol (2ml) and stirring for 30min a sat. aq. NaCl solution (200ml) was added. The mixture was extracted with ethyl acetate (3 x 150ml) and the combined organic layers were washed with sat. aq. NaCl solution (100ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatograped over silicagel using ethyl acetate/ethanol (20:1 and 10:1) as eluent. The product was then crystallized from diethyl ether .

Yield: 0.30g (43% of theory); white crystals

^{1}H-NMR (200 MHz, DMSO-d_6): 2.15 (s, 3H), 3.61 (s, 3H), 3.65 (q, 2H, J=6Hz), 4.12 (t, 2H, J=6 Hz), 6.94-7.22 (m, 7H), 7.72 (d, 1H, J=8 Hz), 7.80 (dd, 1H, J=5 and 0.5 Hz), 8.09 (d, 1H, J=0.5Hz), 8.71 (t, 1H, J=6 Hz), 13.1 (br s, 1H);

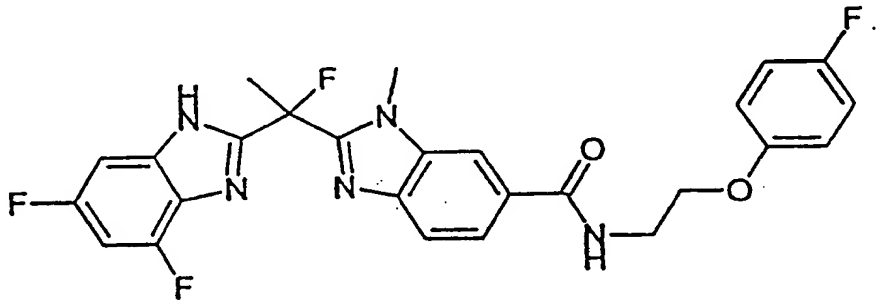
MS (DCI/NH_3) $C_{26}H_{22}F_3N_5O_3$ m/e calc 509.5; found 510 (MH^+);

mp 218 °C;

R_f 0.46 (ethyl acetate / ethanol = 40/3).

Example 55

2-[1-Fluoro-1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide.



To a suspension of example 54 (280mg; 0.550mmol) in dichloromethane (40ml) was added dropwise under argon at -30°C diethylaminosulfurtrifluoride (177mg; 1.01mmol) and stirring was continued for 18h at -20°C - -30°C and for 2h at -5°C - 0°C. The mixture was washed with a sat. aq. $NaHCO_3$ solution (20ml). The aqueous layer was extracted with dichloromethane (20ml) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (20ml), sat. aq. NaCl (20ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatograped over silicagel using ethyl acetate as eluent.

Yield: 227mg (81% of theory); white crystals

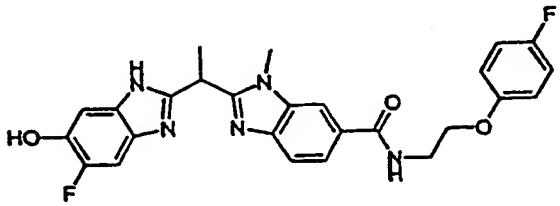
^{1}H-NMR (400 MHz, DMSO-d_6): 2.38 (d, 3H, J=21Hz), 3.68 (q, 2H, J=6Hz), 3.75 (s, 3H), 4.12 (t, 2H, J=6 Hz), 6.95-7.35 (m, 6H), 7.76 (d, 1H, J=8 Hz), 7.84 (dd, 1H, J=5 and 0.5 Hz), 8.20 (d, 1H, J=0.5Hz), 8.75 (t, 1H, J=6 Hz), 13.6 and 13.8 (2 br s, 1H);

MS (ESI) $C_{26}H_{21}F_4N_5O_2$ m/e calc 511.5; found 512.3 (MH^+);

R_f 0.73 (ethyl acetate / ethanol = 40/3).

Example 56

2-[1-(5-Fluoro-6-hydroxy-1*H*-benzimidazol-2yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide.



The preparation was carried out in analogy to example 5 starting from example 26A.

Yield: 73% of theory.

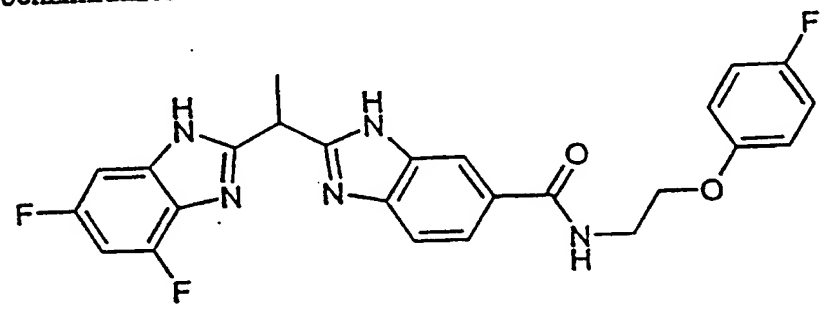
^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (d, 3H, J=7 Hz), 3.65 (q, 2H, J=6Hz), 3.80 (s, 3H), 4.12 (t, 2H, J=6 Hz), 4.97 (q, 1H, J=7 Hz), 6.90-7.22 (m, 5H), 7.28 (d, 1H, J=10Hz), 7.65 (d, 1H, J=8 Hz), 7.76 (dd, 1H, J=5 and 0.5 Hz), 8.10 (d, 1H, J=0.5Hz), 8.68 (t, 1H, J=6 Hz), 9.3 and 9.5 (2 br s, 1H), 12.1 and 12.2 (2 br s, 1H);

MS (ESI) $C_{26}H_{23}F_2N_5O_3$ m/e calc 491.5; found 492.1 (MH^+);

R_f 0.40 (dichloromethane / methanol / conc. aq. NH_3 = 9/1/0.1).

Example 57

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3*H*-benzimidazol-5-carboxamide



The preparation was carried out in analogy to example 20 starting from example 22A and example 7A.

Yield: 47% of theory.

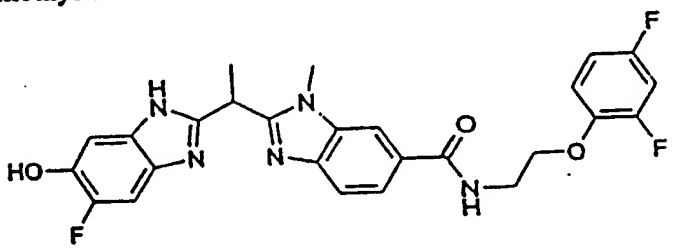
^{1}H-NMR (200 MHz, DMSO-d_6): 1.86 (d, 3H, J=7 Hz), 3.65 (q, 2H, J=6Hz), 4.10 (t, 2H, J=6 Hz), 4.75 (q, 1H, J=7 Hz), 6.94-7.35 (m, 6H), 7.40-7.80 (m, 2H), 7.95-8.20 (m, 1H), 8.68 (br s, 1H), 12.65, 12.70, 12.86 and 13.18 (4 br s, 2H);

MS (DCI/NH_3) $C_{25}H_{20}F_3N_5O_2$ m/e calc 479.5; found 480 (MH^+);

Rf 0.23 (dichloromethane / ethyl acetate = 2/5).

Example 58

N-[2-(2,4-Difluorophenoxy)ethyl]-2-[1-(5-fluoro-6-hydroxy-1*H*-benzimidazol-2yl)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide.



The preparation was carried out in analogy to example 5 starting from example 25A.

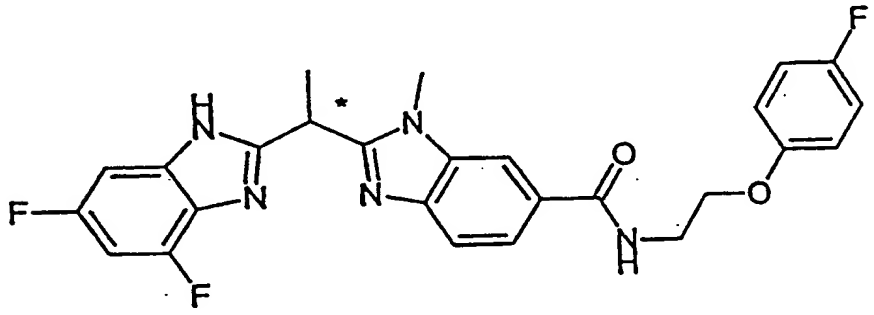
Yield: 91% of theory.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (d, 3H, J=7 Hz), 3.68 (q, 2H, J=6Hz), 3.79 (s, 3H), 4.12 (t, 2H, J=6 Hz), 4.97 (q, 1H, J=7 Hz), 6.90-7.35 (m, 5H), 7.64 (d, 1H, J=8 Hz), 7.76 (dd, 1H, J=5 and 0.5 Hz), 8.10 (d, 1H, J=0.5Hz), 8.72 (t, 1H, J=6 Hz), 9.5 (2 br s, 1H), 12.1 (br s, 1H);
MS (DCI/NH_3) $C_{26}H_{22}F_3N_5O_3$ m/e calc 509.5; found 510 (MH^+);
R_f 0.06 (dichloromethane / ethanol = 20/3).

Example 59 and 60

Example 59: Enantiomer A of 2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide

Example 60: Enantiomer B of 2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



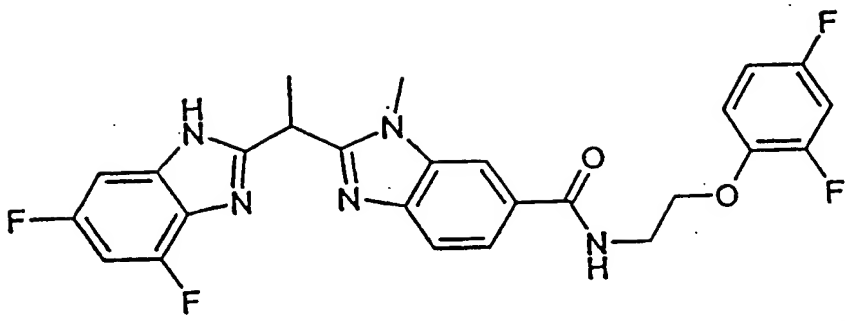
Example 53 (300mg; 0.61mmol) was separated into enantiomers by chiral HPLC (Daicel Chiralpak AS 10µm, 250 x 20 mm, eluent: iso-hexane (85%) / acetonitrile : isopropanol (2:8, 15%); flow 15ml/min; T = 30°C; detection at 230nm)

Enantiomer A: yield: 120mg (40% of theory); white crystalline solid;
enantiomeric excess > 99%
Retention time: 7.11 min

Enantiomer B: yield: 117mg (39% of theory); white crystalline solid;
enantiomeric excess > 98%
Retention time: 8.75 min

Example 61

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(2,4-difluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



The preparation was carried out in analogy to example 20 starting from example 7A and example 21A.

Yield: 54% of theory.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.85 (d, 3H, J=7 Hz), 3.68 (q, 2H, J=6Hz), 3.81 (s, 3H), 4.12 (t, 2H, J=6 Hz), 4.98 (q, 1H, J=7 Hz), 6.95-7.35 (m, 5H), 7.64 (d, 1H, J=8 Hz), 7.76 (dd, 1H, J=5 and 0.5 Hz), 8.10 (d, 1H, J=0.5Hz), 8.71 (t, 1H, J=6 Hz), 13.0 (br s, 1H);

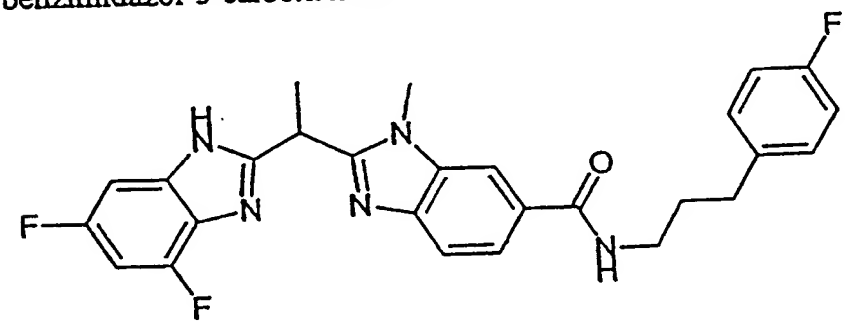
MS (ESI) $C_{26}H_{21}F_4N_5O_2$ m/e calc 511.5; found 512.4 (MH^+);

mp 138-139 °C (dec.).

Rf 0.66 (dichloromethane / methanol = 10/1).

Example 62

2-[1-(4,6-Difluoro-1*H*-benzimidazol-2-yl)ethyl]-*N*-[3-(4-fluorophenyl)propyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 12A and 3-amino-1-(4-fluorophenyl)propane (US 4533655)

Yield: 79% of theory.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.75-1.95 (m, 5H), 2.52 (t, 2H, J=6Hz), 3.30 (m, 3H), 3.81 (s, 3H), 4.98 (q, 1H, J=7 Hz), 6.94-7.30 (m, 6H), 7.62 (d, 1H, J=8 Hz), 7.72 (dd, 1H, J=5 and 0.5 Hz), 8.08 (d, 1H, J=0.5Hz), 8.48 (t, 1H, J=6 Hz), 12.9 (br s, 1H);

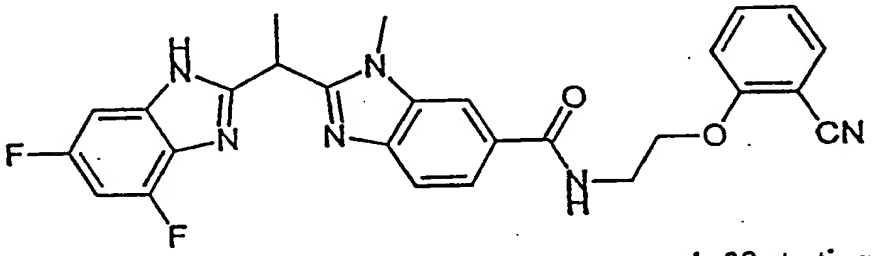
MS (ESI) $C_{27}H_{24}F_3N_5O$ m/e calc 491.5; found 492.2 (MH^+);

m.p. 220-222°C;

Rf 0.24 (dichloromethane / methanol = 20/1).

Example 63

N-[2-(4-Cyanophenoxy)ethyl]-2-[1-(4,6-difluoro-1*H*-benzimidazol-2-yl)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide.



The preparation was carried out in analogy to example 39 starting from example 12A and example 20A.

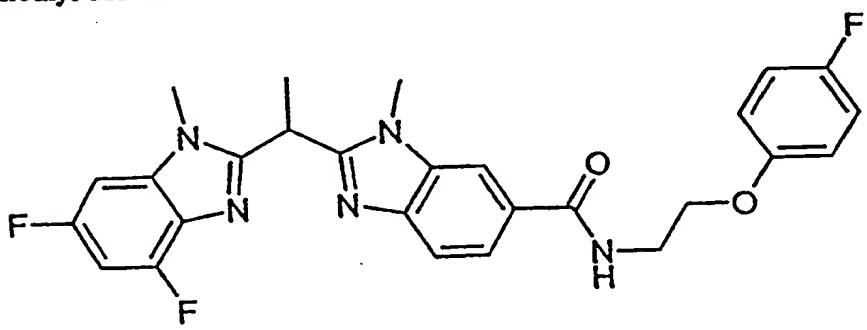
Yield: 82% of theory; white solid.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.85 (d, 3H, J=7 Hz), 3.71 (q, 2H, J=6Hz), 3.81 (s, 3H), 4.33 (t, 2H, J=6 Hz), 4.98 (q, 1H, J=7 Hz), 6.94-7.20 (m, 3H), 7.35 (d, 1H, J=8Hz), 7.60-7.80 (m, 4H), 8.10 (d, 1H, J=0.5Hz), 8.71 (t, 1H, J=6 Hz), 12.9 (br s, 1H);

MS (DCI/NH_3) $C_{27}H_{22}F_2N_6O$, m/e calc 500.5; found 501 (MH^+);

Example 64

2-[1-(4,6-Difluoro-1-methyl-1*H*-benzimidazol-2-yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 30A and example 18A.

Yield: 59% of theory.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (d, 3H, J=7 Hz), 3.65 (s,3H), 3.68 (q, 2H, J=6Hz), 3.78 (s, 3H), 4.12 (t, 2H, J=6 Hz), 5.15 (q, 1H, J=7 Hz), 6.95-7.20 (m, 5H), 7.39 (dd, 1H, J=8 and 1Hz), 7.61 (d, 1H, J=8 Hz), 7.75 (dd, 1H, J=5 and 0.5 Hz), 8.12 (d, 1H, J=0.5Hz), 8.70 (t, 1H, J=6 Hz), 12.9 (br s, 1H);

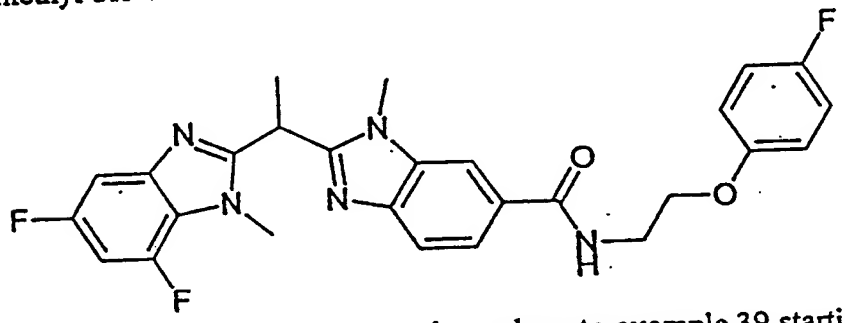
MS (DCI/NH_3) $C_{27}H_{24}F_3N_5O_2$ m/e calc 507.5; found 508 (MH^+);

mp 118 °C;

Rf 0.22 (dichloromethane / methanol = 20/1).

Example 65

2-[1-(4,6-Difluoro-3-methyl-3*H*-benzimidazol-2yl)ethyl]-*N*-[2-(4-fluorophenoxy)ethyl]-3-methyl-3*H*-benzimidazol-5-carboxamide



The preparation was carried out in analogy to example 39 starting from example 31A and example 18A.

Yield: 59% of theory.

^{1}H-NMR (200 MHz, DMSO-d_6): 1.82 (d, 3H, J=7 Hz), 3.65 (q, 2H, J=6Hz), 3.75 (s,3H), 3.81 (s, 3H), 4.12 (t, 2H, J=6 Hz), 5.14 (q, 1H, J=7 Hz), 6.95-7.21 (m, 5H), 7.30 (dd, 1H, J=8 and 1Hz), 7.61 (d, 1H, J=8 Hz), 7.73 (dd, 1H, J=5 and 0.5 Hz), 8.10 (d, 1H, J=0.5Hz), 8.68 (t, 1H, J=6 Hz), 12.9 (br s, 1H);

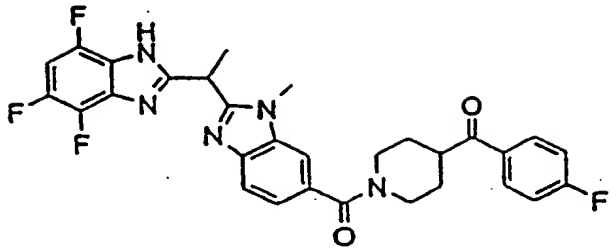
MS (ESI) $C_{27}H_{24}F_3N_5O_2$ m/e calc 507.5; found 508 (MH^+);

mp 232 °C;

Rf 0.61 (dichloromethane / ethanol = 20/1.5).

Example 66

5-[4-(4-Fluorobenzoyl)piperidin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 39 starting from example 11A and 1-(4-fluorobenzoyl)piperidine hydrochloride.

Yield 66% of theory, colorless powder

^{1}H-NMR (300 MHz, DMSO-d_6): 1.82-1.92 (m, 4H), 1.90 (d, 3H, J=7.3 Hz), 3.01-3.14 (m, 2H), 3.44-3.52 (m, 2H), 3.89 (s, 3H), 4.32-4.58 (m, 1H), 4.92 (q, 1H, J=7.2 Hz), 6.81-6.91 (m, 1H), 7.16 (t, 2H, J=8.6 Hz), 7.33 (dd, 1H, J=1.4, 8.3 Hz), 7.53 (d, 1H, J= 0.7 Hz), 7.72 (d 1H, J=8.3 Hz), 7.96-8.01 (m, 2H), 12.20 (br s, 1H);

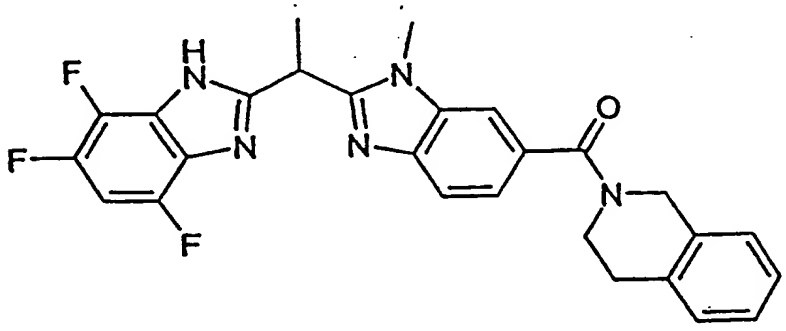
MS (ESI) $C_{30}H_{25}F_4N_5O_2$ m/e calc 563.6; found 564 (MH^+);

mp 172 °C (dec.);

Rf 0.44 (ethyl acetate / methanol = 10/1).

Example 67

3-Methyl-5-(1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl-2-[1-(4,6,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



The preparation was carried out in analogy to example 39 starting from example 11A and 1,2,3,4-tetrahydroisoquinoline.

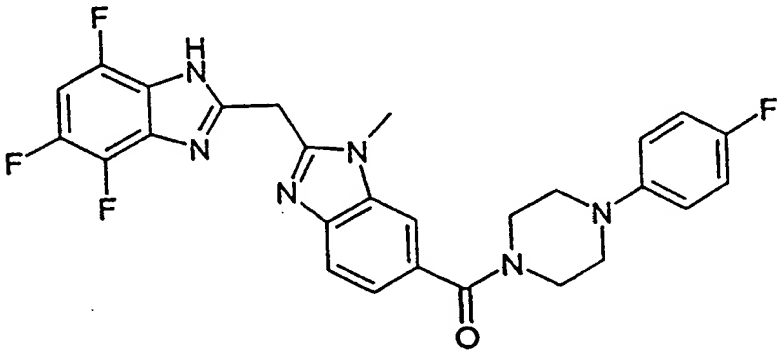
^{1}H-NMR (300 MHz, $CDCl_3$): 1.91 (d, 3H, J=7.3), 2.94 (br s, 2H), 3.50 - 4.12 (br s, 2H), 3.88 (s, 3H), 4.58 -4.95 (br s, 2H),4.92 (q, 1H, J=7.3 Hz), 6.82 - 6.91 (m, 1H), 7.18 (br s, 4H), 7.39 (dd, 1H, J=8.3, 1.5 Hz), 7.56 (s, 1H), 7.77 (d, 1H, J=8.3Hz), 12.06 (br s, 1H);

MS (ESI) $C_{27}H_{22}F_3N_5O$ m/e calc 489.5; found 490 (MH^+);

mp 231 - 232 °C (dec.); Rf 0.24 (ethyl acetate / methanol = 9 / 1).

Example 68

5-[4-(4-Fluorophenyl)piperazin-1ylcarbonyl]-3-methyl-2-[(4,5,7-trifluoro-1H-benzimidazol-2-yl)methyl]-3H-benzimidazole



To a cooled (0 °C), stirred suspension of example 11A (0.50 g, 1.388 mmol) in *N,N*-dimethylformamide (10 mL) was added 1-(4-fluorophenyl)piperazine (0.26 g, 1.457 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.29 g, 1.527mmol), 1-hydroxybenzotriazole (0.24 g, 1.804 mmol) and N-methylmorpholine (0.18g, 1.735 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated in vacuo, the residue was taken up in water and crude product was collected by filtration. Purification was carried out by silica gel column chromatography (dichloromethane / methanol = 100 : 7 as eluent) to give 5-[4-(4-fluorophenyl)piperazin-1ylcarbonyl]-3-methyl-2-[(4,5,7-trifluoro-1H-benzimidazol-2-yl)methyl]-3H-benzimidazole (0.510g) as a slightly brown solid. A sample (310mg) was recrystallized from ethanol.

Yield: 0.223g (30% of theory), grey crystals.

^{1}H-NMR (200 MHz, DMSO-d_6): 3.12 (cm, 4H), 3.68 (cm, 4H), 3.88 (s, 3H), 4.65 (s, 2H), 6.95-7.43 (m, 6H), 7.62 (d, 1H, J=8Hz), 7.70 (d, 1H, J=0.5Hz), 13.65 (br s, 1H);

MS (DCI/NH_3) $C_{27}H_{22}F_4N_6O$ m/e calc 522.5; found 523 ($M+H^+$);

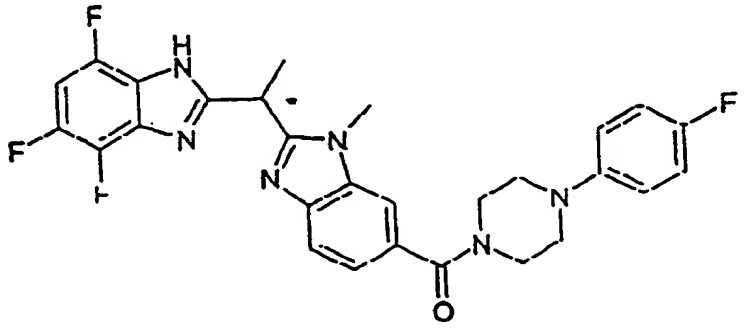
m.p. >250°C ;

Rf 0.59 (dichloromethane / methanol = 100:7).

Examples 69 and 70

Example 69: Enantiomer A of 5-[4-(4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole

Example 70: Enantiomer B of 5-[4-(4-fluorophenyl)piperazin-1-ylcarbonyl]-3-methyl-2-[1-(4,5,7-trifluoro-1*H*-benzimidazol-2-yl)ethyl]-3*H*-benzimidazole



Example 6 (200 mg; 0.373 mmol) was separated into enantiomers by chiral HPLC (Daicel Chiralpak AS 10 µm, 250 x 20 mm, cluent: iso hexane (85%) acetonitrile : isopropanol (2:8, 15%), flow 10 ml/min; T - 25°C; detection at 225 nm)

Enantiomer A: yield 83 mg (40% of theory); white crystalline solid;

enantiomeric excess > 98.5%

Retention time 6.57 min.

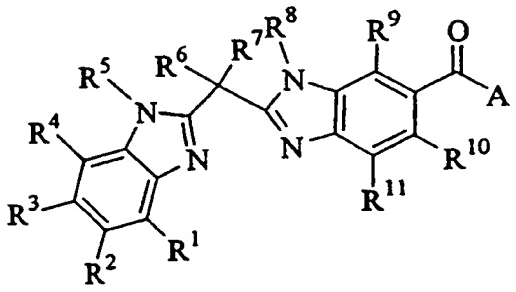
Enantiomer B: Yield: 91 mg (43% of theory); white crystalline solid;

enantiomeric excess > 98.5%

Retention time 9.25 min.

CLAIMS

1. A compound of the general formula (I)



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or halogen,

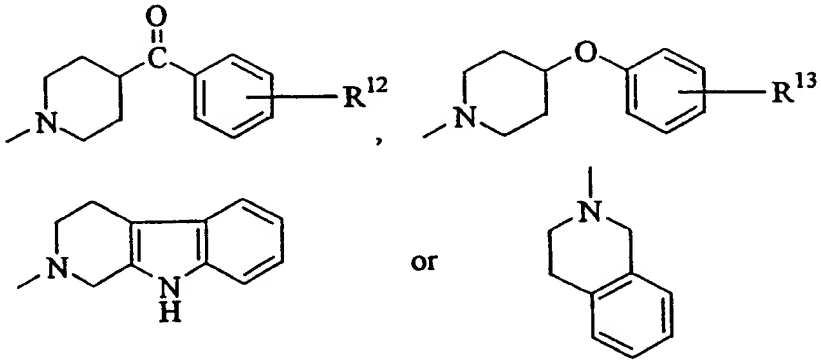
R^5 and R^8 are identical or different and represent hydrogen, straight-chain or branched (C_1-C_4)-alkyl,

R^6 and R^7 are identical or different and represent hydrogen, straight-chain or branched (C_1-C_6)-alkyl, hydroxy, halogen, or straight-chain or branched (C_1-C_6)-alkoxy,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen, halogen, nitro, cyano or trifluoromethyl,

and

A represents a residue of the formula



wherein

R^{12} and R^{13} are identical or different and denote hydrogen, halogen, nitro, cyano, straight-chain or branched (C_1 - C_6)-alkyl or (C_1 - C_6)-alkoxy, or hydroxy,

or

A represents a non-aromatic 5- to 7-membered N-heterocycle which is bound over the nitrogen atom and which optionally contains an oxygen atom or a residue -NR^{14} or -CH-R^{15},

wherein R^{14} and R^{15} are identical or different and denote hydrogen, $(C_3 - C_8)$-cycloalkyl, or denotes straight-chain or branched $(C_1 - C_4)$-alkyl, which is optionally substituted by $(C_6 - C_{10})$-aryl,

or denote $(C_6 - C_{10})$-aryl or a 5- or 6-membered aromatic or non-aromatic heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O, and which, in the case of the non-aromatic heterocycle, is optionally bound over the nitrogen atom and wherein the aryl and the heterocycle are optionally mono- to tri-substituted by identical or different substitutents from the series comprising halogen, nitro, cyano, hydroxy, trifluormethyl or a residue of the formula $-NR^{16}R^{17}$,

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched $(C_1 - C_4)$-alkyl or $(C_1 - C_4)$ acyl, or $-SO_2-CF_3$, or R^{16} and R^{17} form together with the nitrogen atom a non-aromatic 5- to 7-membered heterocycle, optionally further having an oxygen atom or -NH,

or

R^{14} denotes a residue of the formula $-SO_2-R^{18}$,

in which

R^{18} denotes $(C_6 - C_{10})$-aryl, or straight-chain or branched $(C_1 - C_4)$-alkyl,

or

A represents a residue of the formula $-NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen or straight-chain or branched $(C_1 - C_4)$-alkyl,

R^{20} denotes a residue of the formula $-D-E-R^{21}$,

in which

D denotes a straight-chain or branched $(C_1 - C_6)$-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes $(C_6 - C_{10})$-aryl or a 5- or 6-membered aromatic heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O,

which are optionally mono- to tri-substituted by nitro, cyano, halogen, tetrazolyl or by a residue of the formula $-NR^{22}R^{23}$,

in which

R^{22} and R^{23} are identical of different and denote hydrogen, straight-chain or branched

(C_1 - C_6)-acyl or (C_1 - C_6)-alkyl, or R^{22} denotes hydrogen and R^{23} denotes $-SO_2-CF_3$,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt.

2. A compound as claimed in claim 1

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or fluorine,

wherein at least one of the above mentioned substituents R^1, R^2, R^3 or R^4 is different from hydrogen,

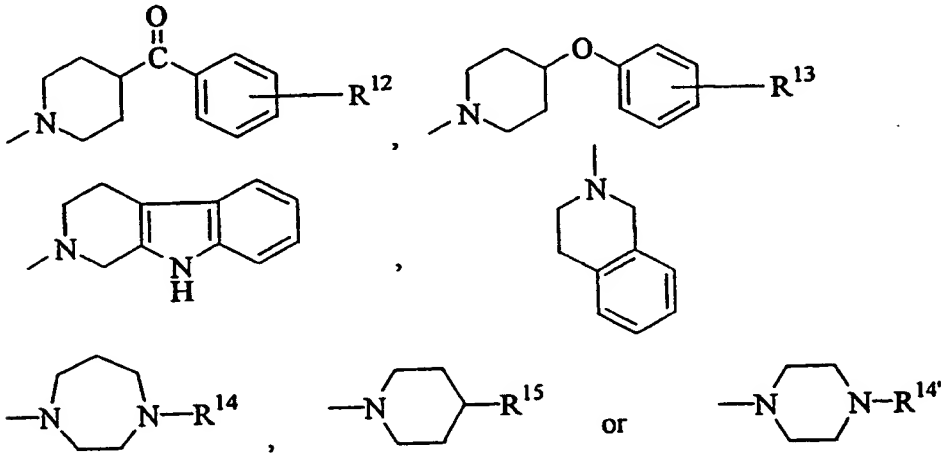
R^5 and R^8 are identical or different and represent hydrogen, methyl, ethyl or isopropyl,

R^6 and R^7 are identical or different and represent hydrogen, straight-chain or branched (C_1-C_4)-alkyl, hydroxy, or fluorine,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen, fluorine, chlorine or cyano,

and

A represents a residue of the formula



wherein

R^{12} and R^{13} are identical or different and denote hydrogen, fluorine, chlorine or cyano,

R^{14}, $R^{14'}$ and R^{15} are identical or different and denote hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or denote straight-chain or branched (C_1 - C_3)-alkyl, which is optionally substituted by phenyl,

or denote phenyl, pyrimidyl, pyridyl or piperidinyl, which are optionally substituted by fluorine, chlorine, nitro, cyano or a residue of the formula $-NR^{16}R^{17}$,

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_3)-alkyl or (C_1 - C_3)-acyl, or -SO_2-CF_3,

or

R^{14} denotes a residue of the formula -SO_2-R^{18},

in which

R^{18} denotes phenyl, or straight-chain or branched (C_1 - C_3)-alkyl,

or

A represents a residue of the formula -$NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen, or straight-chain or branched (C_1 - C_3)-alkyl

and

R^{20} denotes a residue of the formula D-E-R^{21},

in which

D denotes a straight-chain or branched (C_1 - C_5)-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes phenyl or pyridyl, which are optionally monosubstituted or disubstituted by nitro, cyano, fluorine, chlorine, tetrazolyl or by a residue of the formula -$NR^{22}R^{23}$,

in which

R^{22} and R^{23} are identical of different and denote hydrogen, straight-chain or branched (C_1 -C_3)-acyl, or R^{22} denotes hydrogen and R^{23} denotes -SO_2-CF_3,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt.

3. A compound as claimed in claim 1

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or fluorine,

wherein two or three of the above mentioned substituents R^1, R^2 R^3 or R^4 are different from hydrogen,

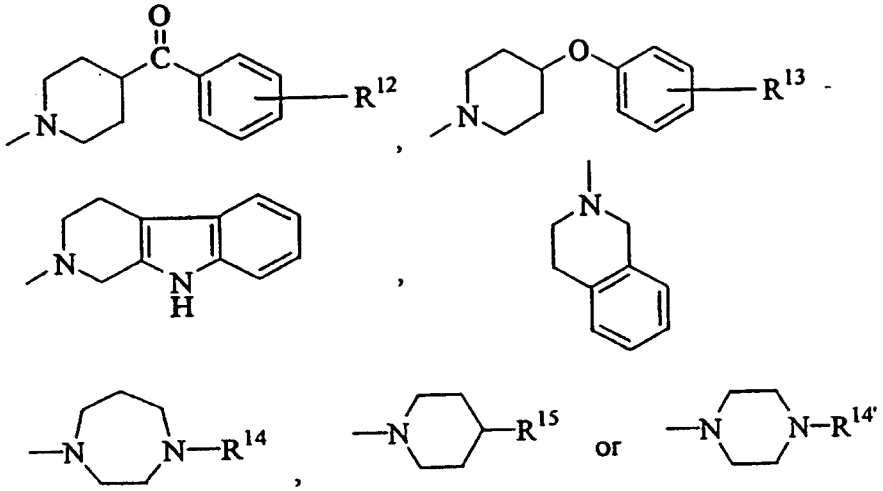
R^5 and R^8 are identical or different and represent hydrogen, methyl or isopropyl,

R^6 and R^7 are identical or different and represent hydrogen, or straight-chain or branched (C_1 - C_3)-alkyl, hydroxy, or fluorine,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen or fluorine,

and

A represents a residue of the formula



wherein

R^{12} and R^{13} are identical or different and denote hydrogen or fluorine

and

R^{14}, $R^{14'}$ and R^{15} are identical or different and denote hydrogen, cyclopentyl, cyclohexyl, cycloheptyl, or denote straight-chain or branched (C_1 - C_3)-alkyl, which is optionally substituted by phenyl, or denote phenyl, pyrimidyl, pyridyl or piperidinyl, which are optionally substituted by fluorine, nitro, cyano or residue of a formula -$NR^{16}R^{17}$,

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_3)-alkyl, or -SO_2-CF_3,

or

$R^{14'}$ denotes a residue of the formula -SO_2-R^{18},

in which

R^{18} denotes phenyl or methyl,

or

A represents a residue of the formula -$NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen or methyl

and

R^{20} denotes a residue of the formula -D-E-R^{21},

in which

D denotes a straight-chain or branched (C_1 - C_4)-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes phenyl or pyridyl, which are optionally monosubstituted or disubstituted by nitro, cyano, fluorine, tetrazolyl or by a residue of the formula $-NR^{22}R^{23}$,

in which

R^{22} and R^{23} are identical or different and denote hydrogen, straight-chain or branched (C_1 - C_3)-acyl, or R^{22} denotes hydrogen and R^{23} denotes $-SO_2-CF_3$,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt.

4. A compound as claimed in claim 1

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen or fluorine,

wherein two or three of the above mentioned substitutents R^1, R^2, R^3 or R^4 are different from hydrogen,

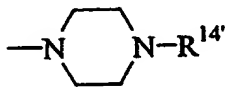
R^5 denotes hydrogen and R^8 denotes methyl,

R^6 and R^7 are identical or different and represent hydrogen, methyl or fluorine,

R^9, R^{10} and R^{11} are hydrogen,

and

A represents a residue of the formula



wherein

$R^{14'}$ denotes phenyl which is optionally substituted by fluorine, cyano or $-NHSO_2CF_3$,

or

A represents a residue of the formula $-NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen,

R^{20} denotes a residue of the formula $-D-E-R^{21}$,

in which

D denotes $(CH_2)_2$-,

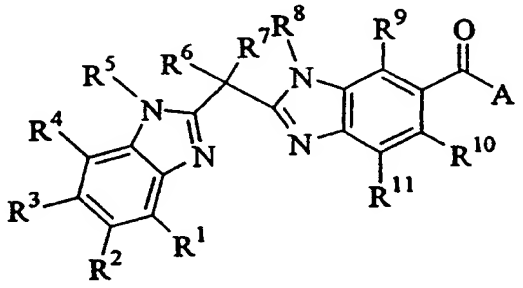
E denotes an oxygen atom

and

R^{21} denotes phenyl which is optionally monosubstituted or disubstituted by fluorine or cyano,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt.

5. A process for the preparation of a compound of the general formula (I)



(I)

in which

R^1, R^2, R^3 and R^4 are identical or different and represent hydrogen, hydroxy or halogen,

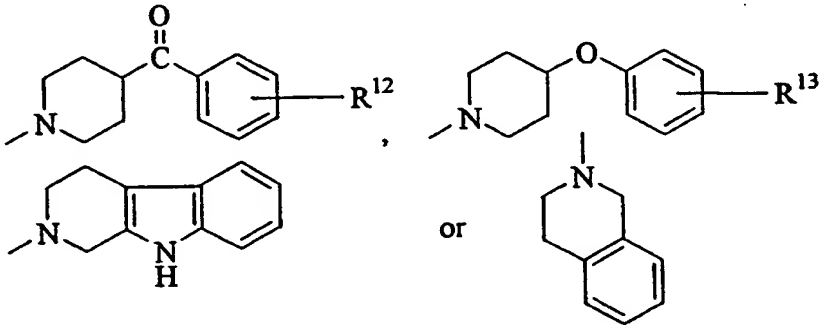
R^5 and R^8 are identical or different and represent hydrogen, or straight-chain or branched (C_1-C_4)-alkyl,

R^6 and R^7 are identical or different and represent hydrogen, straight-chain or branched (C_1-C_6)-alkyl, hydroxy, halogen, or straight-chain or branched (C_1-C_6)-alkoxy,

R^9, R^{10} and R^{11} are identical or different and represent hydrogen, halogen, nitro, cyano or trifluoromethyl,

and

A represents a residue of the formula



wherein

R^{12} and R^{13} are identical or different and denote hydrogen, halogen, nitro, cyano, straight-chain or branched (C_1 - C_6)-alkyl or (C_1 - C_6)-alkoxy, or hydroxy,

or

A represents a non-aromatic 5- to 7-membered N-heterocycle which is bound over the nitrogen atom and which optionally contains an oxygen atom or a residue -NR^{14} or -CH-R^{15},

wherein R^{14} and R^{15} are identical or different and denote hydrogen, (C_3 - C_8)-cycloalkyl, or denotes straight-chain or branched (C_1 - C_4)-alkyl, which is optionally substituted by (C_6 - C_{10})-aryl,

or denote (C_6 - C_{10})-aryl or a 5- or 6-membered aromatic or non-aromatic heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O, and which, in the case of the non-aromatic heterocycle, is optionally bound over the nitrogen atom and wherein the aryl and the heterocycle are optionally mono- to tri-substituted by identical or different substitutents from the series comprising halogen, nitro, cyano, hydroxy, trifluormethyl or a residue of the formula -NR^{16} R^{17},

in which

R^{16} and R^{17} are identical or different and denote hydrogen, straight-chain or branched (C_1- C_4)-alkyl or (C_1 - C_4) acyl, or -SO_2-CF_3, or R^{16} and R^{17} form together with the nitrogen atom a non-aromatic 5- to 7-membered heterocycle, optionally further having an oxygen atom or -NH,

or

R^{14} denotes a residue of the formula -SO_2-R^{18},

in which

R^{18} denotes (C_6 - C_{10})-aryl, or straight-chain or branched (C_1 - C_4)-alkyl,

or

A represents a residue of the formula -$NR^{19}R^{20}$,

in which

R^{19} denotes hydrogen, or straight-chain or branched (C_1 - C_4)-alkyl,

R^{20} denotes a residue of the formula -D-E-R^{21},

in which

D denotes a straight-chain or branched (C_1 - C_6)-alkyl chain,

E denotes an oxygen atom or a bond

and

R^{21} denotes (C_6 - C_{10})-aryl or a 5- or 6-membered aromatic heterocycle having up to 3

heteroatoms from the series comprising N, S and/or O,

which are optionally mono- to tri-substituted by nitro, cyano, halogen, tetrazolyl or by a residue of the formula $-NR^{22}R^{23}$,

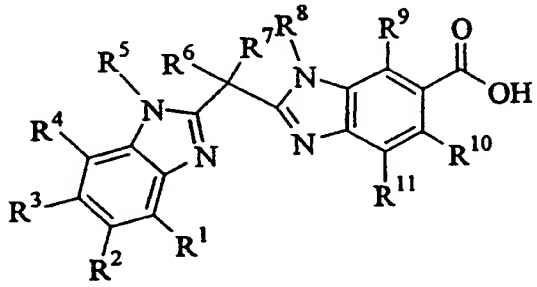
in which

R^{22} and R^{23} are identical of different and denote hydrogen, straight-chain or branched $(C_1 - C_6)$-acyl or $(C_1 - C_6)$-alkyl, or R^{22} denotes hydrogen and R^{23} denotes $-SO_2-CF_3$,

or its salt

comprising that

[A] a compound of the general formula (II)



(II)

in which

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} have the above mentioned meaning,

or its reactive derivative on the carboxyl radical

is reacted in an inert solvent with a compound of the general formula (III)

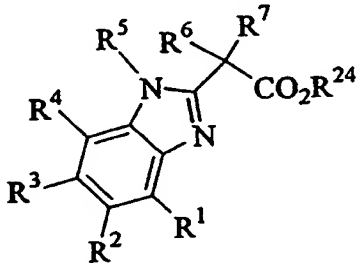
$$A - H \qquad \text{(III)}$$

in which

A has the above mentioned meaning,

or

[B] a compound of the general formula (IV)



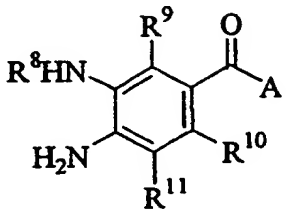
(IV)

in which

R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the above mentioned meaning, and R^{24} denotes straight-chain

or branched (C_1 - C_6)-alkyl,

is reacted in an inert solvent with a compound of the general formula (V)



(V)

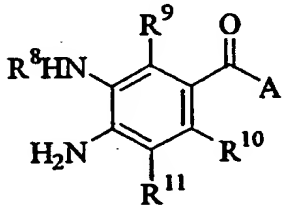
in which

R^8, R^9, R^{10}, R^{11} and A have the above mentioned meaning,

or

[C] in the case where R^6 and R^7 are fluorine in the general formula (I),

first a compound of the general formula (V)

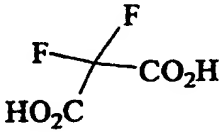


(V)

in which

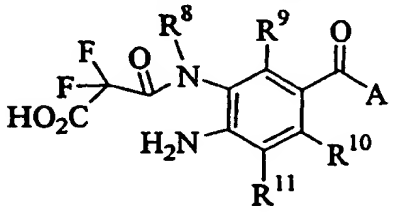
R^8, R^9, R^{10}, R^{11} and A have the above mentioned meaning,

is reacted with a compound of the formula (VI)

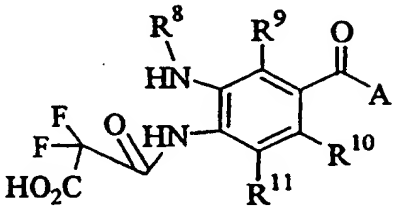


(VI)

together with the system consisting of reagents which can facilitate this reaction in an inert solvent to prepare a compound of the general formula (VIIa and/or VIIb)



(VIIa)

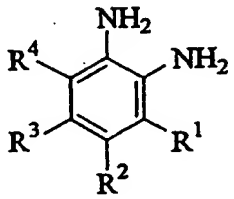


(VIIb)

in which

R^8, R^9, R^{10}, R^{11} and A have the above mentioned meaning,

and in the second step is reacted with a compound of the general formula (VIII)



(VIII)

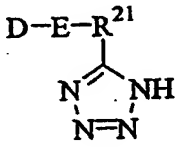
in which

R^1, R^2, R^3 and R^4 have the above mentioned meaning,

with the above mentioned system and finally with acetic acid,

or

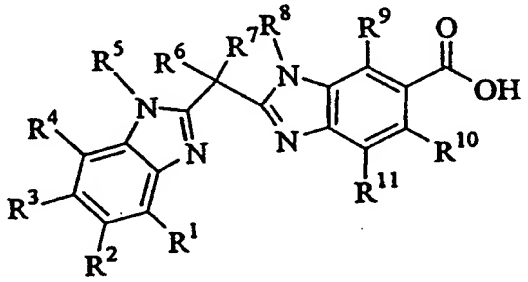
[D] in the case where A in the general formula (I) is a residue of the formula $-NR^{19}R^{20}$ in which R^{19} is hydrogen and R^{20} is a residue of the following formula



in which

D, E and R^{21} have the above mentioned meaning,

a compound of the general formula (II)



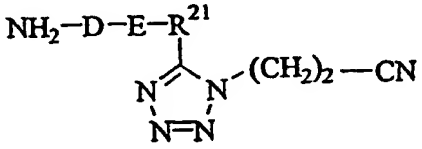
(II)

in which

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} have the above mentioned meaning,

or its reactive derivative on the carboxyl radical

is reacted in an inert solvent with a compound of the general formula (IX)

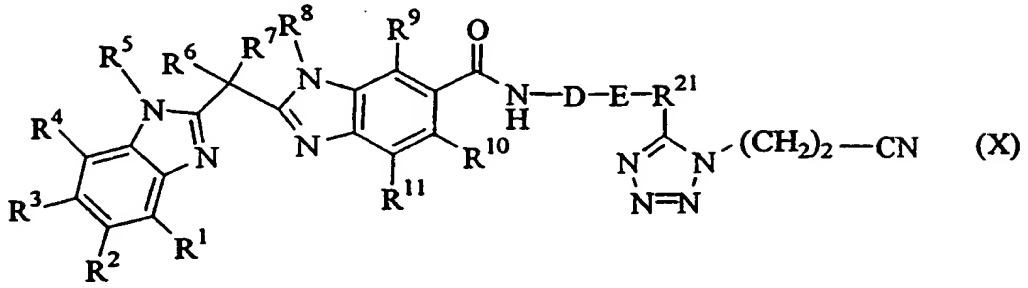


(IX)

in which

D, E and R^{21} have the above mentioned meaning,

to prepare a compound of the general formula (X)



(X)

in which

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{21}, D and E have the above mentioned meaning,

and in the last step the residue $-(CH_2)_2-CN$ is eliminated in the presence of a base,

or

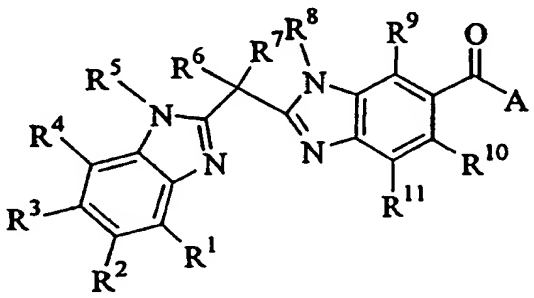
[E] in the case where R^6 is fluorine or hydroxy and R^7 is alkyl in the general formula (I),

a compound of the general formula (I) in which R^6 is hydrogen and R^7 is alkyl,

is reacted first in the system of $NaIO_4$ and $RuCl_3$ in an inert solvent to prepare a compound of the general formula (I), in which R^6 is hydroxy, and optionally in the second step is reacted with $(C_2H_5)_3NSF_3$ in an inert solvent to prepare a fluorine substituted derivative

and further optionally in the case of R^5 and/or R^8 is not hydrogen, followed by alkylation reaction.

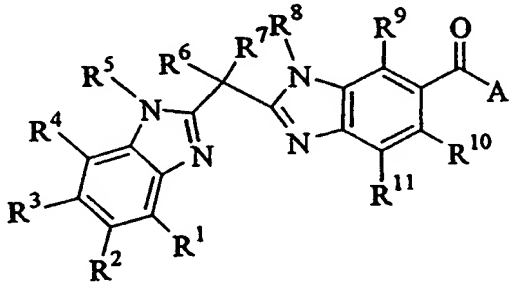
6. A pharmaceutical composition containing a compound of the general formula (I)



(I)

in which
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and A are the same meanings defined in claim 1,
or its tautomeric or stereoisomeric form, or its physiologically acceptable salt as an active ingredient and a pharmaceutically acceptable carrier.

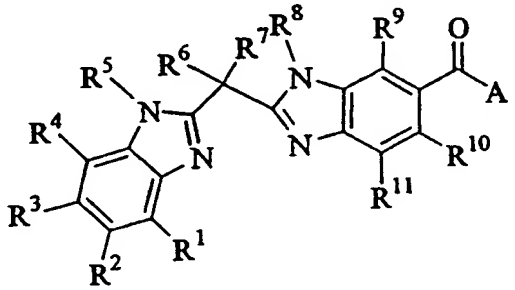
7. A method of treating diseases associated with tryptase activity which comprises administering to a patient an effective amount of a compound of the general formula (I)



(I)

in which
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and A are the same meanings defined in claim 1,.
or its tautomeric or stereoisomeric form, or its physiologically acceptable salt.

8. A method of treating asthma, allergic rhinitis, allergic conjunctivitis or allergic dermatitis which comprises administering to a patient an effective amount of a compound of the general formula (I)

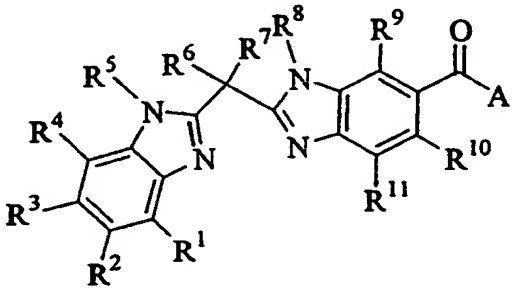


(I)

in which
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and A are the same meanings defined in claim 1,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt.

9. Use of a compound of the general formula (I)



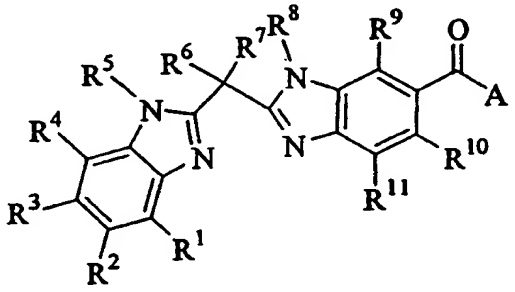
(I)

in which

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and A are the same meanings defined in claim 1,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt for treating diseases associated with tryptase activity.

10. Use of a compound of the general formula (I)



(I)

in which

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and A are the same meanings defined in claim 1,

or its tautomeric or stereoisomeric form, or its physiologically acceptable salt for treating asthma, allergic rhinitis, allergic conjunctivitis or allergic dermatitis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 99/05319

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 99/05319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508540 A	30-03-1995	AU 7661594 A	10-04-1995
		EP 0720603 A	10-07-1996
		HU 71345 A	28-11-1995
		JP 9506335 T	24-06-1997
		ZA 9407352 A	22-03-1996
US 5693515 A	02-12-1997	US 5925553 A	20-07-1999
		US 5900371 A	04-05-1999
WO 9845275 A	15-10-1998	AU 5895098 A	30-10-1998
WO 9926932 A	03-06-1999	AU 1607199 A	15-06-1999

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 99/05319

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/20 C07D403/14 C07D401/14 C07D471/04 A61K31/4184
A61K31/437 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAUGHEY G H ET AL: "BIS(5-AMIDINO-2-BENZIMIDAZOLYL)METHANE AND RELATED AMIDINES. ARE POTENT, REVERSIBLE INHIBITORS OF MAST CELL TRYPTASES" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,US,AMERICAN SOCIETY FOR PHARMACOLOGY AND, vol. 264, no. 2, page 676-682 XP002064911 ISSN: 0022-3565 the whole document	1,6-10
Y	WO 95 08540 A (THE WELLCOME FOUNDATION LIMITED) 30 March 1995 (1995-03-30) claims; example 8	1,6-10

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 1999	17/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 693 515 A (CLARK JAMES M ET AL) 2 December 1997 (1997-12-02) the whole document	1,6-10
Y	KATZ BRADLEY A ET AL: "DESIGN OF POTENT SELECTIVE ZINC-MEDIATED SERINE PROTEASE INHIBITORS" NATURE,GB,MACMILLAN JOURNALS LTD. LONDON, vol. 391, page 608-612 XP002095430 ISSN: 0028-0836 the whole document	1,6-10
P,X	WO 98 45275 A (AXYS PHARMACEUTICALS CORP) 15 October 1998 (1998-10-15) claims	1-10
P,X	WO 99 26932 A (AXYS PHARMACEUTICALS INC) 3 June 1999 (1999-06-03) claims	1-10